NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Aflibercept (Zaltrap®) for the treatment of metastatic colorectal cancer (mCRC) previously treated with an oxaliplatin containing regimen

Submitted by Sanofi UK

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Abbreviations

5-FU	5-fluorouracil
A&E	accidents and emergency
AE	adverse event
AFFIRM	Study of Aflibercept and Modified FOLFOX6 as First-Line Treatment in Patients With Metastatic Colorectal Cancer
AIC	Akaike information criterion
AIO	irinotecan/FU/folinic acid
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMD	age-related macular degeneration
ASCO	American Society of Clinical Oncology
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian information criterion
BSA	body surface area
BSC	best supportive care
CapeOX	oxaliplatin + capecitabine
CC	colon cancer
CE	cost-effectiveness
CEAC	cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval

CONSORT	Consolidated Standards of Reporting Trials
CRC	colorectal cancer
CT	chemotherapy
DET	data extraction table
DMC	data monitoring committee
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5-dimension health questionnaire
ESMO	European Society of Medical Oncology
EU	European Union
FA	folinic acid
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
FOLFIRI	fluorouracil/leucovorin/irinotecan
FOLFOX	folinic acid/5-fluorouracil/oxaliplatin
FOLFOX4	leucovorin 200 mg/m2 as a 2-hour infusion, followed by bolus 5-fluorouracil 400 mg/m2 and a 22-hour infusion of 5-fluorouracil 600 mg/m2 for 2 consecutive days every 14 days, plus a 2-hour infusion of 85 mg/m2 of oxaliplatin on day 1, given simultaneously with leucovorin
FOLFOX6	oxaliplatin (day 1, 100 mg/m2) with leucovorin (400 mg/m2 [racemic] or 200 mg/m2 [L-form]) plus 5-fluorouracil (400 mg/m2 bolus plus 2,400 mg/m2 as a 46-hour continuous infusion) every 2 weeks
G-CSF	granulocyte-colony stimulating factor
GI	gastrointestinal
GP	general practitioner
HLT	high-level term
HR	hazard ratio
HRG	Healthcare Resource Groups
HRQL	health-related quality of life
HTA	health technology assessment
HUI	Health Utility Index
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IFL	irinotecan, leucovorin, fluorouracil
IFU	information for use

IRC	independent review committee
IRIS	irinotecan and S-1 (tegafur, 4-chloro-2, 4-dihydroxypyridine, and potassium oxonate)
IrMdG	irinotecan modified de Gramont
IROX	irinotecan + oxaliplatin
ITT	intention-to-treat
IV	intravenous
IVRS	interactive voice response system
KM	Kaplan-Meier
KOL	key opinion leader
KRAS	Kirsten rat sarcoma viral oncogene homolog
LDH	lactate dehydrogenase
LOS	length of stay
LY	life-year
LYG	life-year gained
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings
NA	not available; not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHS	National Health Service
NHSRC	National Schedule of Reference Costs
NICE	National Institute for Health and Clinical Excellence
NR	not reported
ONS	Office of National Statistics
OPCS	The Office of Population Censuses and Surveys, now named the Office for National Statistics
OPCS-4	Statistical Classification of Surgical Operations version 4
ORR	overall response rate
OS	overall survival
PbR	payment by results
PCT	primary care trust
PenTAG	Peninsula Technology Assessment Group
PFS	progression-free survival
PIGF	placental growth factor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	performance status

PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	preferred term
PTK/ZK	PTK 787/ZK 222584 (vatalanib)
Q2W	every 2 weeks
Q3W	every 3 weeks
QALY	quality-adjusted life-year
QoL	quality of life
QW	once weekly
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RR	risk ratio
RTI-HS	RTI Health Solutions
SAE	serious adverse event
SD	standard deviation
SE	standard error
SF-36	Short-Form 36-Item Health Survey
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SOC	system organ class
SPC	summary of product characteristics
STA	single technology appraisal
TA	technology appraisal
TTO	time tradeoff
TTP	time to progression
Tx	treatment
UK	United Kingdom
ULN	upper limit of normal
US	United States
USA	United States of America
VANILLA	Aflibercept (VEGF Trap) Plus Gemcitabine Versus Placebo Plus Gemcitabine For The First-Line Treatment Of Metastatic Pancreatic Cancer
VAS	visual analogue scale
VAT	value-added tax
VCVM	variance-covariance matrix
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

VELOUR	Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Colorectal Cancer After Failure of an Oxaliplatin Based Regimen
VITAL	Aflibercept and docetaxel versus docetaxel alone after platinum failure in patients with advanced or metastatic non-small cell lung cancer
WE	Western Europe
XELOX	capecitabine/oxaliplatin

Executive summary

Aflibercept is a novel anti-angiogenic agent that targets multiple angiogenic pathways and is licensed for the treatment of adults with mCRC that is resistant to or has progressed after an oxaliplatin-containing regimen. Aflibercept is the only anti-angiogenic agent to demonstrate a significant improvement in survival in the second-line setting in combination with FOLFIRI, the current UK standard of care. Aflibercept plus FOLFIRI significantly improved overall survival, progression-free survival and response rate in comparison with FOLFIRI plus placebo in a double-blind, Phase III trial.

Disease background

Colorectal cancer is the third most common cancer in the UK (ONS 2012), causing ~16,000 deaths annually (Cancer Research UK). One quarter of cases are diagnosed at the metastatic stage, and approximately 50% of cases will progress to become metastatic (Kantar Health 2010).

The current standard of care for metastatic colorectal cancer that is unsuitable for resection is combination chemotherapy. NICE guidelines (CG131) recommend oxaliplatin-based chemotherapy (e.g. FOLFOX) for first-line treatment followed by irinotecan-based regimens (e.g. FOLFIRI) for second-line therapy unless contraindicated.

There is a high unmet need in the second-line setting. Second-line patients have a poor prognosis with a median overall survival of around 12-18 months. To date, no biologics have demonstrated cost-effectiveness and been approved by NICE in the second-line setting.

Angiogenesis

Angiogenesis (formation of new blood vessels) plays a critical role in the growth and migration of solid tumours (Wagner 2009). The most important signalling factors in angiogenesis are the vascular endothelial growth factor (VEGF) ligands. This family of ligands (including VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor [PlGF]) exert their effect through receptors including VEGFR-1 and VEGFR-2 and VEGFR-3 (El Zouhairi et al., 2011). There is thus a clear biological rationale for therapies that target VEGF pathways, and bevacizumab, a monoclonal antibody against VEGF-A, has demonstrated clinical efficacy in cancer. However, angiogenesis is a complex process involving multiple factors and pathways. It is thought that resistance to anti-VEGF-A therapy can develop through compensatory upregulation of other pro-angiogenic factors such as PlGF and VEGF-B, which have both been implicated in pathologic angiogenesis (Papadopoulos 2012).

Aflibercept mechanism of action

Aflibercept is a fully human, recombinant fusion protein that consists of VEGFR extracellular domains (VEGFR-1 and VEGFR-2) fused to the Fc portion of human immunoglobulin G1. Aflibercept acts as a decoy receptor that binds to VEGF ligands in a novel “trap” mechanism. Once bound to aflibercept, VEGF ligands are unable to bind to and activate their cognate receptors.

As detailed below, in comparison with existing anti-angiogenic agents, aflibercept binds to a broader spectrum of pro-angiogenic factors, binds to VEGF-A with higher affinity, and does not form immune complexes; these three properties may confer clinical advantages.

- In addition to binding to VEGF-A with high affinity, aflibercept was designed to also bind to both PlGF and VEGF-B. Because aflibercept binds to these ligands as well as to VEGF-A it may be less prone to drug resistance resulting from the upregulation of other angiogenic factors [Fischer 2008]).
- Aflibercept binds VEGF-A with an approximately 100-fold higher affinity than other VEGF antagonists such as bevacizumab [Holash et al. 2002; Riely and Miller 2007; Papadopoulos et al. 2012]). Aflibercept binding is also more rapid (77-fold faster association rate than bevacizumab) (Papadopoulos 2012).
- Aflibercept forms a stable 1:1 bond with human VEGF-A, human PlGF, or human VEGF-B, to create complexes with no detectable biological and/or immunological activity (Holash et al., 2002; Riely et al., 2007; Rudge et al., 2007), in contrast to anti-VEGF-A antibodies which form multimeric immune complexes that are posited as a potential cause of adverse events (Rudge 2007).

Aflibercept indication and dosing

Aflibercept in combination with FOLFIRI chemotherapy received marketing authorisation in the European Union (EU) on 1st February 2013 for the treatment of adults with mCRC that is resistant to or has progressed after an oxaliplatin-containing regimen.

Aflibercept is administered as an intravenous (IV) infusion over 1 hour every 2 weeks (cycle) at a dose of 4 mg/kg of body weight alongside a standard FOLFIRI regimen. The treatment cycle is repeated every 2 weeks until disease progression or unacceptable toxicity.

Aflibercept is formulated as a solution for injection (25 mg/mL) and is supplied in sealed, sterile, single-use vials. Two aflibercept 25-mg/mL solution presentations are available: (1) 100 mg/4 mL in a 5-mL vial, and (2) 200 mg/8 mL in a 10-mL vial.

The acquisition cost is £295.65 for the 100 mg vial and £591.30 for the 200 mg vial. A patient access scheme with a simple discount is currently being reviewed by the Department of Health and is applied in the cost-effectiveness analyses.

Aflibercept Clinical Evidence

The pivotal VELOUR trial (EFC10262) compared aflibercept plus FOLFIRI with FOLFIRI plus placebo. This was an international, randomised, double-blind, parallel-arm, phase 3 study in 1,226 patients. The primary endpoint was overall survival (OS), with progression-free survival (PFS) and overall response rate (ORR) as secondary endpoints.

Results from the VELOUR Trial showed:

Aflibercept significantly improved overall survival:

- Median OS was increased by 1.44 months in the aflibercept plus FOLFIRI group compared with FOLFIRI plus placebo (13.50 months vs. 12.06 months, respectively; HR, 0.817; 95% CI: 0.713-0.937; $P = 0.0032$).
- Survival curves diverged early and continued to diverge beyond the median. This is reflected in the comparative survival rates at different timepoints. At 24 months, 50% more patients were alive in the aflibercept arm - 28.0% in the aflibercept arm versus 18.7% in the FOLFIRI arm. At 30 months, 22.3% were alive in the aflibercept arm versus 12.0% in the FOLFIRI arm (an 85% increase). This continued separation of the Kaplan-Meier curves is consistent with a sustained benefit of treatment experienced by some patients.

- Mean OS was increased by an estimated 4.7 months, representing an increase of over 25% in the expected survival duration (according to the log-logistic function which provided the best statistical and visual fit).

Aflibercept significantly improved PFS:

- Median PFS was increased by 2.23 months in the aflibercept plus FOLFIRI group compared with FOLFIRI plus placebo (HR 0.758; 95% CI: 0.661 to 0.869; $P < 0.0001$).

Aflibercept produced significantly higher response rates:

- The overall response rate was 19.8% (95% CI: 16.4 to 23.2) in the aflibercept plus FOLFIRI arm compared with 11.1% (95% CI: 8.5 to 13.8) in the FOLFIRI plus placebo arm ($P < 0.001$).

Safety:

The adverse events observed with aflibercept plus FOLFIRI were generally reversible and manageable using current clinical practice. There were two main types of AEs; those typical of the FOLFIRI regimen and which are managed routinely by oncologists treating CRC (the incidences of which were increased in the aflibercept arm), and those typical of anti-angiogenic agents as a class. The majority of grade 3 – 4 events occurred during early treatment cycles and many common AEs occurred only once (Van Cutsem 2011).

Aflibercept Economic Evidence

The submission considers the cost-effectiveness of aflibercept plus FOLFIRI versus FOLFIRI alone, consistent with the NICE scope and the licensed indication for aflibercept. The model is a lifetime Markov model based on three states: stable disease, progressive disease, and dead. The stable disease health state is further subpartitioned into "*On second-line treatment"* and "*Discontinued second-line treatment".*

Probabilities for disease progression and death in the model were calculated according to parametric survival functions for PFS and OS fitted to patient-level data from the VELOUR trial. Probabilities of adverse events came from the VELOUR trial. Resource use data came from a UK retrospective observational study for secondary care and a physician survey for community and social care. Utility data came from an observational study of patients with mCRC undergoing second-line treatment in the UK and Netherlands.

In addition to the main trial population two subgroups were also evaluated; namely the prespecified subgroup of patients with liver-only metastases, and a post-hoc subgroup of patients that excluded those who had received oxaliplatin-based adjuvant therapy and relapsed on or within 6 months of this (this group has been reported in the SmPC).

Results are shown in Table 1 including the patient access scheme; the base-case ICER was £36,294.

Cost-effectiveness results:

Base-case cost-effectiveness results

ITT Population	Aflibercept + FOLFIRI	FOLFIRI
Total costs	[redacted]	[redacted]
Difference in total costs	£8,816	[redacted]
LYG	[redacted]	[redacted]
LYG difference	0.3378	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	0.2429	[redacted]
ICER	£36,294	—
FOLFIRI, irinotecan/5-fluorouracil/folinic acid; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life-years gained; QALY, quality-adjusted life-year.		

In scenario analyses the ICER ranged from £32,729 to £49,805 per QALY. Probabilistic sensitivity analysis (PSA) showed that the probability of aflibercept plus FOLFIRI being cost-effective was 89.5% at a willingness-to-pay threshold of £50,000 per QALY.

In the subgroup of patients with liver-only metastases the ICER was £30,474. In the subgroup of patients that excluded patients who relapsed on or within 6 months of adjuvant therapy the ICER was £32,480.

End-of-life status

It is estimated that approximately 4,000 patients in England and Wales are eligible for second-line treatment following oxaliplatin-based first-line therapy (ONS 2011; Welsh Cancer Intelligence and Surveillance Unit) Expected survival in the second-line indication is considerably less than 24 months; in the placebo arm of VELOUR, median OS was 12.06 months and mean OS was 18.1 months. The mean OS gain with aflibercept was estimated as 4.7 months.

Conclusion

To date, none of the biologic therapies for mCRC have been considered cost-effective by NICE in the second-line setting and it is estimated that approximately 30 – 40% of the Cancer Drugs Fund is currently being allocated to these agents to support English patients with mCRC who have no other effective options. Therefore, there is a clear unmet need for a cost-effective biologic therapy in second-line mCRC.

Aflibercept not only improved mean OS by an estimated 4.7 months, but also produced significant and clinically meaningful improvements in PFS and overall response rate in patients with second-line mCRC, with a safety profile similar to other anti-angiogenic agents. Aflibercept is a novel VEGF-trap, which is the only anti-angiogenic agent to show an OS benefit in the second-line setting in combination with FOLFIRI. Aflibercept is also the first anti-angiogenic to show a benefit in patients with mCRC who have been treated with an oxaliplatin-based therapy and the first anti-angiogenic therapy to show benefit in patients with mCRC previously treated with another anti-angiogenic therapy. The consistent divergence of the survival curves beyond the median indicates that some patients

experience a prolonged benefit which may be due to the activity of aflibercept on multiple angiogenic factors.

In the end-of-life setting, the mean OS improvement provided by aflibercept represents an increase of more than 25% in life expectancy for these patients. With the inclusion of a patient access scheme, the ICER for aflibercept is £36,294, indicating aflibercept can be considered a cost-effective treatment.

Section A – Decision problem

1 Description of technology under assessment

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

Brand name: Zaltrap™

Approved name: Aflibercept

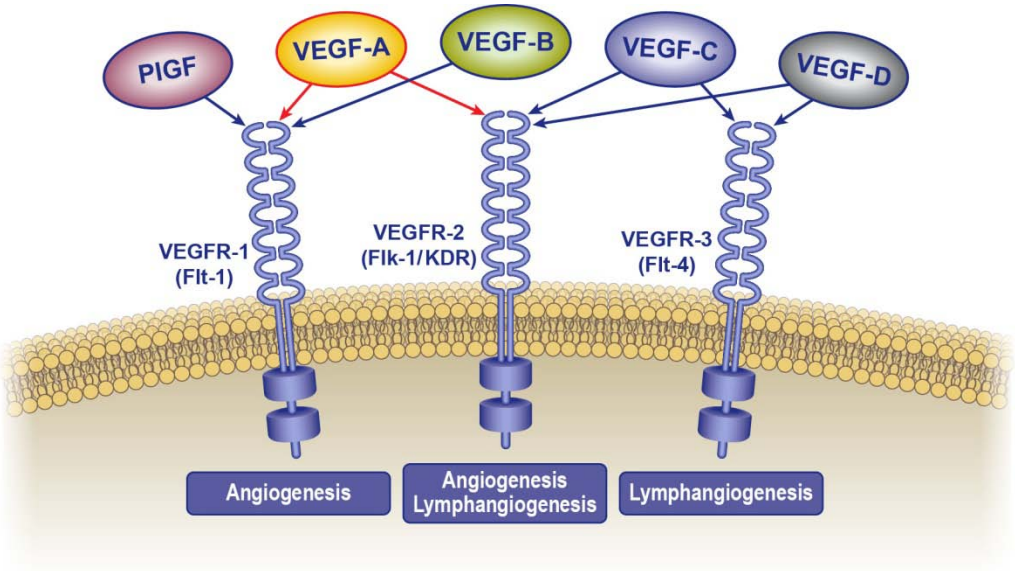
Therapeutic class:

L	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
L01	ANTINEOPLASTIC AGENTS
L01X	OTHER ANTINEOPLASTIC AGENTS
L01XX	Other antineoplastic agents
L01XX44	Aflibercept

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

Angiogenesis (formation of new blood vessels) plays a critical role in the growth and migration of solid tumours (Escudero-Esparza et al., 2009). The vascular endothelial growth factor (VEGF) ligands are critically important signalling factors in angiogenesis. This family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF) and bind to receptors, including VEGFR-1, VEGFR-2, and VEGFR-3 (El Zouhairi et al., 2011). Binding of VEGF ligands to their cognate receptors on the surface of blood vessel endothelial cells affects downstream signalling pathways to control endothelial cell survival, proliferation, and migration (Figure A-1) (Wagner et al., 2009; Tol and Punt, 2010; El Zouhairi et al., 2011).

Figure A-1. The VEGF family and its receptors



Source: Neufeld et al., 1999.

Tumour cells release pro-angiogenic factors to stimulate blood vessel formation. Therefore, there is a clear biological rationale for therapies that target VEGF, and indeed bevacizumab, which is a monoclonal antibody against VEGF-A, has demonstrated efficacy in colorectal cancer. However resistance to anti-angiogenic therapy can occur through compensatory upregulation of other pro-angiogenic factors (e.g., PlGF), a process termed *angiogenic rescue* (Fischer et al., 2008).

Aflibercept is a novel, fully human, recombinant fusion protein that consists of VEGFR extracellular domains (VEGFR-1 and VEGFR-2) fused to the Fc portion of human immunoglobulin G1. Aflibercept acts as a decoy receptor that blocks the VEGF pathway by preferentially binding to VEGF ligands in a novel “trap” mechanism.

Aflibercept binds to VEGF-A with approximately 100-fold higher affinity than bevacizumab (Holash et al. 2002; Riely and Miller 2007; Papadopoulos et al. 2012). This higher affinity also results in faster binding—the association rate was 77-fold faster than bevacizumab in one study (Papadopoulos 2012).

In addition to binding VEGF-A, aflibercept also binds to VEGF-B and PlGF. Both VEGF-B and PlGF play a limited role in normal vascular development but are implicated in pathologic angiogenesis (Papadopoulos et al., 2012). The activity of aflibercept against multiple pro-angiogenic factors may mean aflibercept is less susceptible to drug resistance than agents that target only one angiogenic factor (Papadopoulos et al., 2012).

Furthermore, pharmacodynamic studies show that aflibercept forms a stable 1:1 bond with human VEGF-A, human PlGF, and human VEGF-B, to form a complex that has no detectable biological and/or immunological activity (Holash et al., 2002; Riely et al., 2007; Rudge et al., 2007). This is in contrast to the multimeric immune complexes formed with bevacizumab, which are proposed to contribute to certain specific adverse events (AEs) such as thrombosis (through platelet activation)

and potentially also renal damage (through tissue deposition in the kidney) (Rudge et al., 2007; Meyer et al., 2009).

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

Aflibercept—in combination with fluorouracil, leucovorin, and irinotecan (FOLFIRI)—has a UK marketing authorisation for the treatment of adults with metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen. The UK marketing authorisation was received on the 1 February 2013.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

[redacted]

The CHMP concluded that the risk-benefit balance of aflibercept in combination with FOLFIRI chemotherapy in the treatment of adults with mCRC that is resistant to or has progressed after an oxaliplatin-containing regimen is favourable. Therefore, the CHMP recommended the granting of the marketing authorisation subject to the following conditions:

- Periodic safety update reports
- Obligation to complete post-authorisation measures—the EMA has requested that Sanofi analyse plasma and tissue samples from the available trials, with the primary aim of identifying biomarkers, to allow better selection of the population likely to experience a beneficial effect following treatment with aflibercept, thereby optimising the benefit-risk balance.

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

The approved indication is as follows:

Aflibercept in combination with irinotecan/5 fluorouracil/folinic acid (FOLFIRI) chemotherapy is indicated in adults with metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen.

Unrelated to this marketing authorisation, approval for an alternative formulation of aflibercept has been sought by Bayer Schering and Regeneron (Eylea™ solution for intravitreal injection for the treatment of age-related macular degeneration [AMD]). In November 2012, the EMA granted marketing authorisation for Eylea 40 mg/ml solution for injection intended for the treatment of neovascular (wet) AMD.

The route of administration and dosing of aflibercept in the treatment of AMD (0.5 mg administered by intravitreal injection every 4 weeks or 2 mg administered by intravitreal injection every 8 weeks) is very different from that for the treatment of mCRC (4 mg/kg administered intravenously [IV] every 2 weeks).

These treatments are not interchangeable. Sanofi has no involvement in the development of aflibercept for AMD, and that formulation and indication is outside the scope of this submission.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Table A-1 presents completed trials investigating aflibercept in mCRC and Table A-2 summarises ongoing trials (nonrandomised and randomised controlled trials [RCTs]) investigating aflibercept in mCRC that are expected to report in the next 12 months.

Table A-1. List of completed trials of aflibercept in mCRC

Trial number (acronym) phase	Trial design	Interventions	Population	Primary outcome measures	Secondary outcome measures	Reference
EFC10262 (**VELOUR**)	Phase 3, prospective, multicentre, multinational, randomised (1:1), double-blind, placebo-controlled study	Aflibercept 4 mg/kg IV over 1 hour on day 1 every 2 weeks, followed immediately by the FOLFIRI regimen (irinotecan 180 mg/m^2 IV over 90 minutes, with leucovorin 400 mg/m^2 IV over 2 hours, followed by FU 400 mg/m^2 bolus and FU 2,400 mg/m^2 continuous infusion over 46 hours) Matching placebo on day 1 every 2 weeks, followed immediately by the FOLFIRI regimen	Aged ≥ 18 years Histologically or cytologically proven adenocarcinoma of the colon or rectum Metastatic disease not amenable to potentially curative treatment (i.e., inoperable) ECOG PS 0-2 Measurable or nonmeasurable disease Only one oxaliplatin-based prior regimen Progressed during or following the last administration of the oxaliplatin-based chemotherapy or relapsed within 6 months of completion of oxaliplatin-based adjuvant chemotherapy	Overall survival (defined as the time interval from randomisation to death from any cause)	Progression-free survival (defined as the interval from randomisation to the first observation of disease progression or death from any cause) Objective response (complete response and partial response according to RECIST criteria [version 1.0]). Treatment-emergent adverse events and laboratory abnormalities	Van Cutsem et al., 2012

Trial number (acronym) phase	Trial design	Interventions	Population	Primary outcome measures	Secondary outcome measures	Reference
TCD10794 (NCT00921661) Phase 1	Nonrandomised, single-group, dose-escalation, open-label study	Aflibercept + FOLFIRI every 2 weeks	Japanese patients with mCRC aged ≥ 20 years who had received at least one prior line of treatment with any standard of care, who had failed the treatment, or who had not been eligible for standard of care for safety reasons	Dose-limiting toxicity of aflibercept + FOLFIRI	Safety, pharmacokinetics , tumour burden, immunogenicity	Yoshino et al., 2012
CDR0000518293 (NCT00407654) Phase 2	Open-label, phase 2 study	Aflibercept 4 mg/kg IV over 1-2 hours , every 2 weeks, in 2-week cycles Patients split into two arms: 50 who had received prior bevacizumab; 24 who had not received prior bevacizumab	Patients with mCRC, aged ≥ 18 years, with ECOG PS 0-2 or Karnofsky PS 60%-100%, and had received ≥ 1 prior systemic chemotherapy for metastatic disease and had documented radiological or clinical progression after the most recent therapy	Combination of objective response rate and 16-week progression-free survival	Toxicity; overall survival	Tang et al., 2012
EFC10668 (AFFIRM)	Phase 2, randomised, non-comparative, open-label study	Modified FOLFOX6 Modified FOLFOX6 + aflibercept	First-line mCRC[a] with ECOG PS 0-2, aged ≥ 18 years (N = 236)	Progression-free survival at 12 months	Overall response rate, progression-free survival, overall survival, biomarkers	Pericay et al., 2012
Phase 1	Double blind, multicentre, randomised, parallel group, placebo-controlled study	Aflibercept 4 mg/kg on day 1, irinotecan-LV5FU2 on days 1 and 2, or Placebo on day 1, irinotecan-LV5FU2 on	Aged ≥ 18 years , ECOG PS 0-2, histologically or cytologically confirmed solid malignancy (metastatic or unresectable or for which no	Safety	Tumour response; pharmacodynamic and pharmacokinetic	Khayat et al., 2013

Trial number (acronym) phase	Trial design	Interventions	Population	Primary outcome measures	Secondary outcome measures	Reference
		days 1 and 2 Followed by all patients receiving aflibercept + LV5FU2 every 2 weeks	conventional therapy existed but for which treatment with irinotecan-LV5FU2 was appropriate) ≥1 measurable lesion amenable to DCE-MRI		endpoints	

AFFIRM, Study of Aflibercept and Modified FOLFOX6 as First-Line Treatment in Patients With Metastatic Colorectal Cancer; FU, fluorouracil; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol 5-dimension health questionnaire; FOLFIRI, fluorouracil/leucovorin/irinotecan; FOLFOX6, fluorouracil/folinic acid/oxaliplatin; FU, fluorouracil; IV, intravenously; mCRC, metastatic colorectal cancer; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTC, National Cancer Institute Common Toxicity Criteria; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; VELOUR, Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Colorectal Cancer After Failure of an Oxaliplatin Based Regimen.

[a] This is for first-line mCRC, which is not the indication of interest for this submission. This study has been included for completeness only.

Table A-2. **List of ongoing trials expected to report in the next 12 months**

Trial number (acronym) phase	Trial design	Interventions	Population	Primary outcome measures	Secondary outcome measures	Date expected to report Reference
AFLIBC06097 (ASQoP) Phase 3	Prospective, phase 3b/4, international, multicentre, single-arm, open-label study	1-hour IV infusion of aflibercept every 2 weeks + FOLFIRI Aflibercept: 4 mg/kg over 1 hour on day 1 followed by FOLFIRI, administered as follows: • dl-Leucovorin: 400 mg/m² over 2-hour infusion on day 1 • Irinotecan: 180 mg/m² over 90-minute infusion on day 1, followed by bolus FU 400 mg/m² and FU continuous infusion 2,400 mg/m² over 46 hours infusion • Or as individualised by physician's clinical judgement • Treatment cycle will be administered every 2 weeks.	Patients with mCRC aged ≥ 18 years, with ECOG PS 0 or 1 and only 1 prior oxaliplatin-based chemotherapeutic regimen for metastatic disease (Estimated enrolment: 900 globally; 50 in the UK)	Safety Treatment-emergent adverse events: • Terminology (according to MedDRA) • Frequency and severity (according to NCI-CTCAE version 4.0) • Seriousness and relatedness • Laboratory abnormalities according to NCI-CTC version 4.0	HRQL assessed by using changes from baseline in scores derived from three HRQL questionnaires: • EORTC QLQ-C30 (version 3) • EORTC QLQ-CR29 (disease-specific supplement to QLQ-C30): optional • EQ-5D (version 4)	Study protocol published: April 2012, Sanofi data on file, 2012a Interim analysis ongoing (cut-off date 5 November 2012). Further interim analyses will be processed and submitted to NICE expected in 2Q 2013

ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol 5-dimension health questionnaire; FOLFIRI, fluorouracil/leucovorin/irinotecan; FU, fluorouracil; HRQL, health-related quality of life; IV, intravenous; mCRC, metastatic colorectal cancer; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTC, National Cancer Institute Common Toxicity Criteria; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; UK, United Kingdom.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

The anticipated launch of aflibercept in the United Kingdom is March 2013.

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

Aflibercept (also known as *ziv-aflibercept*) is licensed in the United States as follows:

> ZALTRAP, in combination with 5-fluorouracil, leucovorin, irinotecan-(FOLFIRI), is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.

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

Sanofi intends to submit a New Product Assessment Form for aflibercept in combination with FOLFIRI chemotherapy in mCRC to the Scottish Medicines Consortium (SMC) in March 2013. Guidance is expected to be published in the summer of 2013.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A-3. **Unit costs of technology being appraised**

Pharmaceutical formulation	25 mg/mL solution for injection in single-use vials Two 25 mg/mL solution presentations are available: 100 mg/4 mL in a 5-mL vial and 200 mg/8 mL in a 10-mL vial
Acquisition cost (excluding VAT)	100 mg vial of aflibercept: £295.65 at list price 200 mg vial of aflibercept: £591.30 at list price [redacted]
Method of administration	Intravenous infusion
Dose	4 mg/kg of body weight administered over 1 hour
Dosing frequency	2-week cycle time
Average length of a course of treatment	In the VELOUR study, patients received a mean of [redacted] of aflibercept plus FOLFIRI regimen over a mean of
Average cost of a course of treatment	Aflibercept plus FOLFIRI [redacted]
Anticipated average interval between courses of treatments	No additional courses of treatment are anticipated
Anticipated number of repeat courses of treatments	No additional courses of treatment are anticipated
Dose adjustments	Dose adjustment and/or cycle delay are planned in case of toxicity
FOLFIRI, fluorouracil/leucovorin/irinotecan; VAT, value-added tax; VELOUR, Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Colorectal Cancer After Failure of an Oxaliplatin Based Regimen.	

1.11 *For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.*

Not applicable.

1.12 *Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?*

There are no additional tests or investigations needed for selection, and there are no particular administration requirements.

1.13 *Is there a need for monitoring of patients over and above usual clinical practice for this technology?*

No additional monitoring of patients is required over and above usual clinical practice for these patients.

1.14 *What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?*

Following administration of aflibercept, all patients will receive the FOLFIRI chemotherapy regimen, administered as follows:

- Irinotecan 180 mg/m^2 IV infusion over 90 minutes and leucovorin (dl racemic) 400 mg/m^2 IV infusion over 2 hours at the same time on day 1 using a Y line, followed by
- 5-Fluorouracil (5-FU) 400 mg/m^2 IV bolus, followed by
- 5-FU 2,400 mg/m^2 continuous IV infusion over 46 hours.

(In practice, FOLFIRI doses may be adapted and the above is only indicative). Administration of aflibercept followed by the FOLFIRI regimen is considered as a single treatment cycle. The treatment cycle is repeated every 2 weeks.

Premedications and concomitant medications associated with the aflibercept/FOLFIRI regimen are discussed in section 2.8.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Pathophysiology

Colorectal cancer is a cancer arising in the large intestine, specifically in the colon or the rectum (American Cancer Society, 2011). Colorectal adenocarcinoma accounts for 95% of CRC cases (Kufe et al., 2003). Colorectal cancer evolves from polyps—precancerous growths—that may be present in either the colon or the rectum (NICE Clinical Guideline, 2011). A small percentage of polyps ultimately undergo malignant transformation over a period of several years (Kufe et al., 2003; American Cancer Society, 2011). Colorectal tumours are often, but not always, confined to the large intestine for a relatively long period of time before penetrating the bowel wall and spreading to lymph nodes and distant sites (Australian Government National Health and Medical Research Council, 2005).

Metastatic disease develops through several distinct steps (Portera et al., 1998; Guo et al., 2004); first, cancer cells detach from neighbouring cells and then they degrade the basement membrane before penetrating into the interstitial stroma. Once the invading cells penetrate the vascular or lymphatic channels cells may detach and be transported within the circulatory system. Tumour emboli that evade the body's immune defences then travel in the circulatory system to arrive at compatible organs, where they embed and proliferate to establish micrometastases. Survival and growth of these micrometastatic lesions requires angiogenesis (i.e., the formation of a blood supply).

Aetiology

Colorectal cancer is caused by genomic instability and the accumulation of multiple tumour-associated mutations (Markowitz and Bertagnolli, 2009). In most CRC cases (approximately 80%), there is no defined hereditary risk factor (Benson et al., 2007). Approximately 20% of patients with CRC have an established family history of the disease or a hereditary CRC syndrome (Benson et al., 2007).

Epidemiology

In the UK, CRC is the third most common cancer in women, after lung and breast cancer, and in men, after prostate and lung cancer (Office of National Statistics [ONS], 2012). Between 2008 and 2010, on average, over 40,000 people were diagnosed with CRC in the UK each year (ONS, 2012).

Approximately one quarter of patients present with metastatic CRC (mCRC) at diagnosis (Kantar Health, 2010). Despite an improvement in disease outcomes arising from improved screening, surgery, and the introduction of modern chemotherapeutics, approximately half of all nonmetastatic CRC cases progress to mCRC. In mCRC, the liver is the most common site of metastasis, with other common sites being the lymph nodes and lungs.

Cancer Research UK indicates that in 2010, there were 16,013 deaths from CRC in the UK (Cancer Research UK, 2012).

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

An estimated 4,028 mCRC patients will be eligible for second-line treatment following oxaliplatin-based first-line therapy in England and Wales in 2013 (ONS, 2011; ONS, 2012). There are no other indications for this technology.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

Information on life expectancy for patients with mCRC shows relatively wide variation. For patients with mCRC diagnosed in the UK in 1996-2002, data from the National Cancer Intelligence Network Lead Cancer Registry for Colorectal Cancer showed a 5-year survival of 6.6% (Cancer Research UK, 2012). However, global survival rates may be changing. A recent review in the US of mCRC survival indicates an increase in the 5-year OS rate (Kopetz et al., 2009). The 5-year OS rate increased from 9.1% for patients diagnosed in 1990-1997 to 13.0% for those diagnosed in 1998-2000 and 19.2% for those diagnosed in 2001-2003. Curative resection of liver metastases appears to have contributed to the improvements in the earlier periods, whereas in the later periods, a significant impact on survival improvements remained after controlling for liver resection rates; the authors suggest this more recent improvement is associated with an increase in the availability of biological agents.

The 5-year survival rate for patients receiving second-line mCRC therapy was estimated by Jemal and colleagues (2008) at 10%; observed median OS ranges between 10.5 to 18 months (Seymour et al., 2011; Jonker et al., 2007; Peeters et al., 2010; Kozloff et al., 2011).

Data from the VELOUR trial indicate that patients receiving FOLFIRI after an oxaliplatin-containing regimen have a median OS of 12.1 months. Approximately 12.0% remained alive at 2.5 years.

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

In June 2004, NICE issued guidance on cancer services in the UK (Guidance on cancer services, improving outcomes in CRC [NICE, 2004]).

A NICE clinical guideline was issued in November 2011 (Clinical guideline 131, colorectal cancer: the diagnosis and management of colorectal cancer [NICE, 2011]).

However, since 2005, of the four technology appraisals published by NICE in this disease area, only one technology—Cetuximab in the first line setting—has received an *optimised* recommendation for patients with mCRC confined to the liver (TA176, 2009).

In the second-line setting, the three newer technologies appraised have not been approved by NICE, namely:

- Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy), and panitumumab (monotherapy) for the treatment of mCRC after first-line chemotherapy (review of TA150 and part review of TA118) (TA242 [NICE, 2012]).

Table A-4 summarises specific subgroups addressed in NICE guidelines and technology appraisals.

Table A-4. Subgroups addressed in NICE guidelines and technology appraisals

Guideline/Technology Appraisal (Date)	Subgroups Considered
Clinical Guideline 131 (November 2011). Colorectal cancer: The diagnosis and management of colorectal cancer	Patients with mCRC who are intolerant to FU/FA or for whom these drugs are not suitable
TA176 (August 2009). Cetuximab for the first-line treatment of mCRC	Patients with KRAS wild-type mCRC and with only nonresectable liver metastases
TA 242 (January 2012): Cetuximab (monotherapy or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy), and panitumumab (monotherapy) for the treatment of mCRC after first-line chemotherapy (review of TA150 and partial review of TA118).	For cetuximab and panitumumab, patients with KRAS wild-type mCRC (analysed retrospectively)
FU/FA, fluorouracil/folinic acid; mCRC, metastatic colorectal cancer; TA, technology appraisal.	

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

The NICE Clinical Guideline 131 recommends the following sequences of chemotherapy when offering an oxaliplatin-based chemotherapy in the first-line setting to patients with advanced and metastatic CRC (NICE, 2011):

- FOLFOX as first-line treatment, then FOLFIRI as second-line treatment
- FOLFOX as first-line treatment, then single-agent irinotecan as second-line treatment
- XELOX (capecitabine plus oxaliplatin) as first-line treatment, then FOLFIRI as second-line treatment.

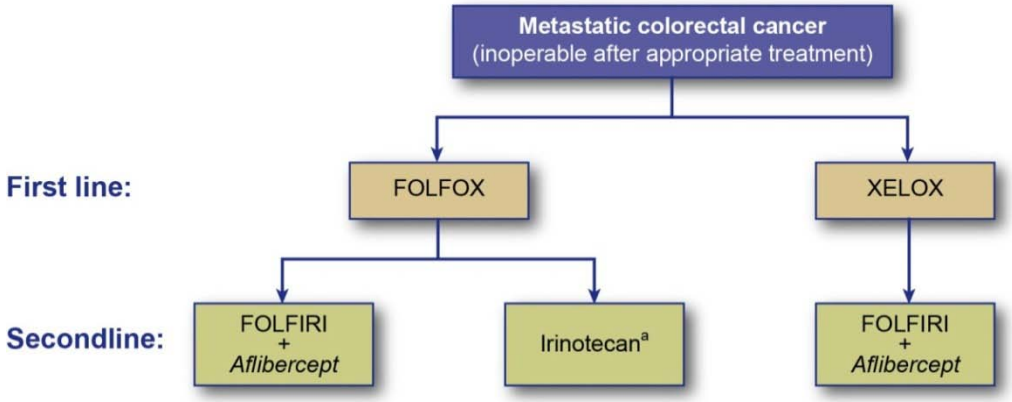
NICE Guideline 131 also notes that raltitrexed should be considered for patients with advanced CRC who are intolerant to 5-fluorouracil and folinic acid or for whom these drugs are not suitable, such as patients who develop cardiotoxicity (NICE, 2011).

FOLFIRI is currently the standard of care for patients able to tolerate second-line combination chemotherapy following FOLFOX.

Irinotecan monotherapy is also recommended as an option for second-line treatment after FOLFOX; however, its use is more limited in the UK. The recommended irinotecan dose is higher when administered as a monotherapy, and the higher dose is associated with greater toxicity than FOLFIRI (Clarke et al., 2011).

The proposed use of aflibercept is + FOLFIRI for the treatment of patients with mCRC previously treated with an oxaliplatin-based regimen. Figure A-2 presents the current typical clinical pathway of care for patients with mCRC, as recommended in NICE Clinical Guideline 131, and includes the proposed place for aflibercept.

Figure A-2. Clinical pathway of care for patients with metastatic colorectal cancer in whom oxaliplatin is given first line



FOLFIRI, folinic acid/5-fluorouracil/irinotecan; FOLFOX, folinic acid/5-fluorouracil/oxaliplatin; XELOX, capecitabine/oxaliplatin.

[a] Irinotecan monotherapy is usually reserved for patients who are not able to tolerate further fluorouracil-based therapy. As such, irinotecan monotherapy is not considered to be a relevant comparator.

Note: NICE Clinical Guideline 131 indicates that raltitrexed should be considered for only patients with advanced CRC who are intolerant to 5-fluorouracil and folinic acid or for whom these drugs are not suitable (e.g., patients who develop cardiotoxicity).

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

There are a variety of regimens containing irinotecan + FU-based therapy that have been used in mCRC, including irinotecan/FU/folinic acid (AIO), irinotecan modified de Gramont (IrMdG), and minor variations of the FOLFIRI regimen. The current National Comprehensive Cancer Network (NCCN) guidelines state that infusional 5-FU regimens are less toxic than bolus regimens and that any bolus regimen of 5-FU is inappropriate when administered with irinotecan. Therefore, the NCCN panel no longer recommends using the irinotecan plus fluorouracil/leucovorin (IFL) regimen (NCCN, 2012).

A 2010 article reported on a literature review and an advisory panel to elicit expert opinion as to the types of therapy containing irinotecan and FU used in mCRC (Shabaruddin et al.,

2010a). The study reported that the IrMdG regimen was the most commonly used in second-line treatment of mCRC in the UK. The IrMdG regimen contains irinotecan 180 mg/m^2 (over 30 minutes), levofolinate 175 mg (over 2 hours), FU 400 mg/m^2 (bolus), and FU 2,400 mg/m^2 (over 46 hours).

The FOLFIRI regimen used in VELOUR was very similar, containing irinotecan 180 mg/m^2 (over 90 minutes), leucovorin (folinic acid) 400 mg/m^2 (over 2 hours), FU 400 mg/m^2 (bolus given over 24 minutes), followed by FU 2,400 mg/m^2 (over 46 hours).

2.7 Please identify the main comparator(s) and justify their selection.

The NICE Clinical Guideline 131 recommends FOLFIRI or irinotecan monotherapy as second-line therapy following first-line oxaliplatin-based therapies (NICE, 2011).

In line with the scope for this technology appraisal, irinotecan monotherapy is not considered to be a relevant comparator for aflibercept plus FOLFIRI; it is not as widely used as FOLFIRI, and because aflibercept is indicated in combination with FOLFIRI, patients eligible for aflibercept must be suitable for second-line FU-based combination chemotherapy.

Oxaliplatin-based regimens are not considered relevant comparators for this appraisal because the licence for aflibercept requires patients to have previously received an oxaliplatin-based regimen; it is inappropriate for these patients to receive oxaliplatin in the second-line setting.

Bevacizumab and cetuximab in combination with FOLFIRI are not recommended by NICE; therefore, in line with the scope for this technology appraisal, these treatments are not considered to be comparators for aflibercept plus FOLFIRI.

Therefore, the only relevant comparator for aflibercept plus FOLFIRI is FOLFIRI alone.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Therapies that may be used to manage adverse reactions associated with the aflibercept and FOLFIRI regimen are listed below. Of these, only anti-hypertensive therapy is particularly linked to aflibercept; the others are all used to manage adverse reactions that can occur with the FOLFIRI regimen alone.

- Intravenous or subcutaneous atropine (0.25-1 mg) may be given to patients who experience cholinergic adverse effects (including early diarrhoea), unless they are contraindicated.
- Prophylactic anti-emetic therapy may be administered.
- Granulocyte-colony stimulating factor (G-CSF) may be administered to patients who experience grade ≥ 3 neutropaenia. Treatment should be initiated upon a first episode, and secondary prophylaxis can be implemented for subsequent treatment cycles.

- Antihypertensives may be required, dependent on the severity of adverse events.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Aflibercept is administered intravenously as a single 1-hour infusion alongside standard FOLFIRI; as such, no additional staffing is required. Aflibercept will be administered within a day-case setting; therefore, inpatient admission and associated facilities are not required.

Based on the HRG code SB14Z, the cost of each administration of aflibercept with FOLFIRI is estimated to be £331, for both the first and subsequent cycles (NHS, 2012). This is the same as the cost of administration for FOLFIRI alone.

Table A-5. Aflibercept: potential service implications

Health care group	Implications
Nursing	Patients will need to be educated about the new treatment and its efficacy and side-effect profile Side effects will need to be managed
Pharmacy services	Minimal aseptic manipulation No specific premedication is required
Pathology, biochemistry, haematology, radiology services	Patients are required to undergo routine monitoring, including blood tests in line with standard practice, and this is already in place for monitoring patients receiving FOLFIRI If required, proteinuria urinalysis by biochemistry laboratory
Primary care services	Adverse events resulting from treatment with aflibercept may be managed in primary care
Source: Van Cutsem et al., 2012; Sanofi data on file, 2012c.	

2.10 Does the technology require additional infrastructure to be put in place?

No additional infrastructure is anticipated to be required.

3 Equality

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- *could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;*
- *could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g., by making it more difficult in practice for a specific group to access the technology*
- *could lead to recommendations that have any adverse impact on people with a particular disability or disabilities*

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

No issues have been identified.

3.1.2 How has the analysis addressed these issues?

Not applicable.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Aflibercept is a novel recombinant fusion protein that has been specifically designed to bind to all human isoforms of VEGF-A, VEGF-B and PlGF, thereby creating a VEGF-signalling blockade (Papadopoulos et al., 2012). As highlighted in section 1.2, aflibercept is the first anti-angiogenic agent to bind all of these factors, which are believed to play important roles in pathologic angiogenesis. In binding VEGF-A, VEGF-B, and PlGF, aflibercept covers a wider spectrum of angiogenic factors than any other agent currently being used in mCRC therapy (Cursiefen et al., 2004; Papadopoulos 2012). This may make it less susceptible to the development of drug resistance than agents that target only one ligand.

Aflibercept binds to VEGF-A with approximately 100-fold higher affinity than bevacizumab and with faster binding kinetics (77-fold faster association rate) (Papadopoulos 2012). In addition, aflibercept forms a stable 1:1 bond with human VEGF-A, human PlGF, or human VEGF-B to form a complex that has no detectable biological and/or immunological activity (Holash et al., 2002; Riely and Miller, 2007; Rudge et al., 2007), thus reducing the risk of side effects. Conversely, bevacizumab binds to VEGF-A to form multimeric immune complexes, which are proposed to contribute to certain adverse events (Rudge et al., 2007).

Aflibercept is the first anti-angiogenic therapy to show an OS benefit in patients with mCRC who have been treated with an oxaliplatin-based therapy, and the only drug to demonstrate a statistically significant OS benefit in combination with FOLFIRI in such patients. Aflibercept is also the first anti-angiogenic therapy to show benefit in patients with mCRC previously treated with another anti-angiogenic therapy.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life-year (QALY) calculation.

There are a number of factors described below that may result in the quality-adjusted life-year (QALY) value calculated for aflibercept failing to capture significant benefits to the patient, carers, and society.

- There may be an important psychological benefit of aflibercept as it provides a further option to allow patients to continue to receive active treatment to control the disease. This may also have benefits for the carers and family of patients.
- The OS data indicate that the survival curves diverge early between the aflibercept plus FOLFIRI and FOLFIRI arms and continue to diverge. This suggests at least some patients may experience a long-term modification of the disease – with the possibility to survive to see further treatment options become available.

- For patients with a poor prognosis, the relative improvement in survival may be valued more highly than the absolute increase in survival. Although the relationship between life expectancy and the societal value placed on incremental survival improvements is still unclear, there may be a greater weight placed by the patient than society on incremental improvements in survival when life expectancy is short.
- The aflibercept molecule was designed to avoid certain adverse events associated with multimeric complex formation within tissues as observed with bevacizumab. In the counterfactual state, if aflibercept did not have this *designed-in* property, we should see more adverse events effects associated with multimeric complex formations; however, it is impossible to test this.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

To fully appreciate the importance to patients and their families of being able to actively fight mCRC in second-line therapy and, as such, the psychological benefit of aflibercept treatment, we believe that the committee should seek the opinions of patients, family members, and clinicians.

5 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with mCRC that is resistant to or has progressed following prior oxaliplatin-based chemotherapy	People with mCRC that that is resistant to or has progressed following prior oxaliplatin-based chemotherapy	
Intervention	Aflibercept + FOLFIRI	Aflibercept + FOLFIRI	
Comparator(s)	Irinotecan + fluorouracil-based therapy	FOLFIRI (Irinotecan + fluorouracil and leucovorin)	FOLFIRI is a regimen that contains irinotecan + fluorouracil-based therapy
Outcomes	Outcome measures to be considered: • Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	The outcome measures considered in the submission include: • Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.	The cost-effectiveness of aflibercept is expressed in terms of incremental cost per QALY. The time horizon for estimating clinical and cost-effectiveness is patients' lifetimes (15 years), to reflect any differences in costs or outcomes between the technologies being compared. Costs are considered from an NHS and PSS perspective.	

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Subgroups to be considered	None identified	Subgroups under consideration: • Patients with metastasis confined to the liver • Subgroup excluding patients progressing on or within 6 months of adjuvant treatment	Patients with liver metastases were a pre-specified subgroup; they have also been recognised previously by NICE as a clinical subgroup in mCRC. The mechanism of action that would favour an improved response in this group is unknown, but the magnitude of treatment effect and the test for interaction was significant. A post hoc analysis of patients progressing within 6 months of adjuvant therapy was accepted by CHMP and is presented in the SmPC.
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation.	None identified	
CHMP, Committee for Medicinal Products for Human Use, FOLFIRI, 5-fluorouracil plus folinic acid (or leucovorin) plus irinotecan; mCRC, metastatic colorectal cancer; NHS, National Health Service, NICE, National Institute for Health and Clinical Excellence, PSS, Personal Social Services, QALY, quality-adjusted life-year; SmPC, Summary of Product Characteristics.			

Section B – Clinical and cost effectiveness

6 Clinical evidence

6.1 Identification of studies

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

A systematic literature review was performed to identify studies evaluating second-line treatment of mCRC.

MEDLINE (via PubMed), Embase, and Cochrane Collaboration Central Register of Clinical Trials (CENTRAL) were searched to identify English-language studies published between 1 January 1992 and 19 December 2012. The searches were conducted using a combination of search terms and keywords for second-line colorectal cancer, treatments of interest, and terms related to the study design (e.g., randomised controlled trial [RCT]).

Proceedings from two conferences (American Society of Clinical Oncology [ASCO] and European Society of Medical Oncology [ESMO]) were also reviewed for relevant abstracts presented at meetings held in 2010, 2011, and 2012. Bibliographies of systematic review articles were examined to obtain additional relevant references. Bibliographies of accepted studies were also reviewed to identify other potentially relevant references.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Table B1 describes the PICOST inclusion and exclusion criteria used to assess studies for the systematic review. The searches included limits for English language and human subjects.

Table B1. **Eligibility criteria used in search strategy**

Clinical effectiveness		
Inclusion criteria	P – Patients	• Adult patients with mCRC
	I – Interventions	• All current second-line chemotherapy regimens including but not limited to: • Bevacizumab • Irinotecan

Clinical effectiveness		
		• FOLFIRI • Bevacizumab + FOLFIRI • Bevacizumab + FOLFOX • FOLFOX4 • FOLFOX6 • CapeOX • XELOX
	C – Comparators	• Placebo • Best supportive care • The same second-line chemotherapy regimen at a different dose level, or the same second-line chemotherapy regimen with additional active chemotherapy agent or adjuvant therapy agent, or another second-line chemotherapy
	O – Outcomes	• Mean/median and HR (with 95% CI and *P* value): OS, PFS, TTP • Number of patients with complete response, partial response, stable disease, and progressive disease • Number of patients discontinuing for any reason, and/or due to AEs • Pre-defined grade 3 and 4 AEs • Quality of Life
	S – Study design	• RCT
	T – Time	• January 1992 to December 2012
Exclusion criteria	P – Patients	• Adults who do not have mCRC
	I – Interventions	• No second-line chemotherapy interventions
	C – Comparators	• No second-line chemotherapy interventions
	O – Outcomes	• No relevant data on any of the outcomes of interest for at least 20 patients per treatment arm or group
	S – Study design	• Studies that are not randomised • Letters to the editor regarding randomised trials • Citations without an abstract • Open-label extensions of an RCT • RCTs where crossover to third-line is permitted and outcomes are not reported prior to the crossover
AE, adverse event; CapeOX, oxaliplatin + capecitabine; CI, confidence interval; FOLFIRI, 5-fluorouracil plus folinic acid plus irinotecan; FOLFOX, 5-fluorouracil plus folinic acid plus oxaliplatin; FOLFOX4, 5-fluorouracil plus folinic acid plus oxaliplatin (same medications as FOLFOX but with different administration schedule); FOLFOX6, 5-fluorouracil plus folinic acid plus oxaliplatin (same medications as FOLFOX but with different administration schedule); HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; TTP, time to progression; XELOX, capecitabine plus oxaliplatin.		

6.2.2 *A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o = 1065).*

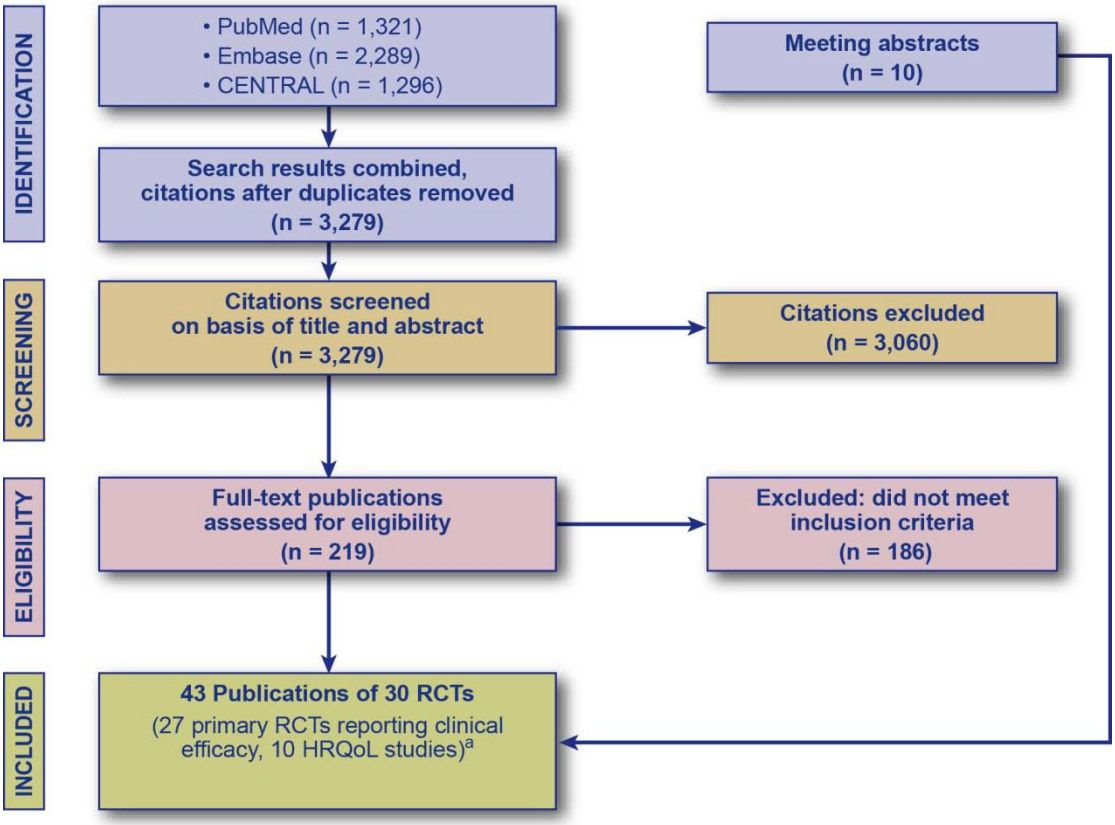
The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

This systematic literature review identified 43 publications of 30 RCTs published since 1992 that evaluated second-line treatment of mCRC. Twenty-seven of the 30 trials investigated clinical efficacy and safety outcomes, and 10 trials evaluated HRQL outcomes (3 trials evaluated only HRQL outcomes and 7 trials evaluated clinical efficacy and safety and HRQL outcomes). Section 10.2.8 in the Appendices provides details of these 30 records.

Figure B-1 describes the study attrition results for quantitative analysis in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-style diagram.

As described in section 6.2.4, only one trial identified had evaluated the intervention under appraisal.

Figure B-1. **Flow diagram of identification process for systematic review**



HRQL = health-related quality of life; RCT = randomised controlled trial.

[a] Among the 10 HRQL studies, 7 were based on data from primary RCTs reporting clinical efficacy and safety. Three unique trials, which reported HRQL only, were also included.

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table B2 presents details of the VELOUR RCT with aflibercept. This was identified in the systematic search as the Van Cutsem et al., 2012 record and as an associated conference abstract. Together with the full publication, data on file have been used to support this dossier.

Table B2. **List of randomised, controlled trials investigating aflibercept**

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
EFC10262 (**VELOUR**)	4 mg/kg aflibercept intravenously (IV) over 1 hour on day 1 every 2 weeks, followed immediately by the FOLFIRI regimen (irinotecan 180 mg/m^2 IV over 90 minutes, with leucovorin 400 mg/m^2 IV over 2 hours, followed by fluorouracil [FU] 400 mg/m^2 bolus and FU 2,400 mg/m^2 continuous infusion over 46 hours) at home[a]	Matching placebo on day 1 every 2 weeks, followed immediately by the FOLFIRI regimen	• Patients aged ≥18 years with histologically or cytologically proven adenocarcinoma of the colon or rectum, with inoperable metastatic disease • ECOG PS 0-2 • Measurable or non-measurable disease • Only one oxaliplatin-based prior regimen for metastatic disease. Patients had to have progressed during or following the last administration of the oxaliplatin-based chemotherapy. Patients who relapsed within 6 months of completion of oxaliplatin-based adjuvant chemotherapy were eligible.	Van Cutsem et al., 2012

ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, 5-fluorouracil + folinic acid (or leucovorin) + irinotecan; IV, intravenous.

[a] Ambulatory: not required to be in hospital.

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

One RCT, Study EFC10262 (VELOUR), compared aflibercept + FOLFIRI with placebo + FOLFIRI in patients with mCRC previously treated with an oxaliplatin-based regimen.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

No RCTs for aflibercept were excluded from further discussion.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

Two non-RCT studies are considered relevant to the decision-problem:

A non-randomised trial currently investigating aflibercept in patients with mCRC (ASQoP) is described in Table A-2. The primary objective of this study is to evaluate the safety of aflibercept in patients with mCRC treated with FOLFIRI after failure of an oxaliplatin-based regimen. The secondary objective is to document the HRQL in this patient population. Results of this study are expected to become available during the course of this appraisal process.

In addition, an observational multi-national, multi-centre, noninterventional cross-sectional utility study ("mCRC utilities study") has also been conducted to estimate utility values for patients on FOLFIRI in the second-line setting; while database checking and queries with sites are still ongoing the majority of the data are complete. This study is described in section 7.4.6.

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, ***the information should be tabulated****.*

Methods

6.3.2 *Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.*

Table B3 presents the design of Study EFC10262 (VELOUR).

Table B3. **Comparative summary of methodology of Study EFC10262 (VELOUR)**

Trial no. (acronym)	**Study EFC10262 (VELOUR)**
Location	176 centres in 28 countries: Argentina, Australia, Austria, Belgium, Brazil, Chile, Czech Republic, Denmark, Estonia, France, Germany, Greece, Italy, Korea, Netherlands, New Zealand, Norway, Poland, Puerto Rico, Romania, Russian Federation, South Africa, Spain, Sweden, Turkey, Ukraine, United Kingdom, United States
Design	Phase 3, prospective, multicentre, multinational, randomised, double-blind, placebo-controlled study
Duration of study	Median follow-up for intent-to-treat population, 22.28 months
Method of randomisation	Eligible patients were randomly assigned 1:1, to receive aflibercept + FOLFIRI (aflibercept arm) or placebo + FOLFIRI (control arm) using a centralised IVRS based on a permuted-block randomisation, stratified according to prior therapy with bevacizumab (yes or no), and ECOG PS (0, 1, or 2).
Method of blinding (care provider, patient and outcome assessor)	• Treatment assignment was performed centrally with the use of an IVRS • Patients, investigators, and other persons responsible for study conduct and data analyses remained blinded to the study treatment assignment • Aflibercept and placebo were supplied in indistinguishable sealed vials in identical boxes corresponding to patient kits • During the course of the study, an external statistician (independent from the Sponsor) performed unblinded safety and efficacy interim analyses for the purpose of data review by the Data Monitoring Committee

Trial no. (acronym)	Study EFC10262 (VELOUR)
Intervention(s) (n =) and comparator(s) (n =)	Patients randomised: • Aflibercept 4 mg/kg + FOLFIRI (n = 612) • Placebo + FOLFIRI (n = 614) Patients randomised and received allocated intervention : • Aflibercept 4 mg/kg + FOLFIRI (n = 604) • Placebo + FOLFIRI (n = 605) Number of patients in the UK: • Aflibercept 4 mg/kg + FOLFIRI (n = 52 [8.5%]) • Placebo + FOLFIRI (n = 47 [7.7%]) Patients were to be treated until occurrence of disease progression or unacceptable toxicity according to physician judgement. Patients could stop one drug but still continue treatment with the other components of the regimen. If FOLFIRI was permanently discontinued, then aflibercept or placebo could be continued until disease progression, unacceptable toxicity, or patient's refusal of further treatment. The end-of-study treatment date was the date of the last aflibercept or placebo administration. If aflibercept or placebo was permanently discontinued, then FOLFIRI could be continued until disease progression, unacceptable toxicity, or patient's refusal of further treatment. The end-of-study treatment date was the date of the last FOLFIRI administration. Any anti-cancer treatment administered after the last study treatment administration until death or until study termination (whichever came first) was documented.
Primary outcomes (including scoring methods and timings of assessments)	See Table Table B5 in section 6.3.5
Secondary outcomes (including scoring methods and timings of assessments)	See Table B5 in section 6.3.5
Duration of follow-up	Following documentation of progressive disease, patients were to be followed for survival status every 2 months until death or withdrawal of patient consent or until the cut-off date for final analysis of OS was reached, whichever came first. Patients who discontinued treatment before disease progression were followed every 6 weeks for PFS. Once progression was documented (according to investigator evaluation), surviving patients were followed every 2 months for survival until death or study cut-off. After data cut-off for primary analysis of OS, patients who were still receiving study treatment and patients who were alive and had completed study treatment, and were experiencing ongoing SAEs or new/ongoing related AEs, were to be followed for safety purposes until stabilisation or resolution for a maximum of 9 months after the study cut-off.

AEs, adverse events; DMC, data monitoring committee; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, fluorouracil/leucovorin/irinotecan; IRC, independent review committee; IV, intravenous; IVRS, interactive voice response system; OS, overall survival; RECIST, Response Evaluation Criteria In Solid Tumours; SAE, serious adverse event.

FOLFIRI regimen: irinotecan 180 mg/m^2 IV infusion over 90 minutes and leucovorin 400 mg/m^2 IV infusion over 2 hours at the same time in bags using a Y-line, followed by 5-FU 400 mg/m^2 IV bolus

given over 2-4 minutes, followed by 5-FU 2,400 mg/m² continuous IV infusion over 46 hours.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Inclusion criteria for Study EFC10262 (VELOUR) were as follows:

- Aged 18 years or older
- ECOG PS of 0 to 2
- Histologically or cytologically proven colorectal adenocarcinoma
- Metastatic disease not amenable to potentially curative treatment
- Measurable or nonmeasurable disease (as per Response Evaluation Criteria In Solid Tumors [RECIST] criteria)
- Only one prior chemotherapeutic regimen for metastatic disease, which had to be an oxaliplatin-containing regimen. Although patients were to have documented progression while on or after completion of a single, prior, oxaliplatin-containing regimen, they were not selected for the timing of their progression. Patients who experienced relapse on or within 6 months of completion of oxaliplatin-based adjuvant therapy were eligible.
- Prior bevacizumab was permitted, prior irinotecan was not.

Randomisation occurred 28 days or more after cessation of prior radiotherapy or chemotherapy and 30 days or more after ending participation in another clinical trial involving an investigational drug. Patients with a history of major surgery within 28 days were not allowed to participate.

Eligible patients had to have no known prior malignancies or known brain metastases; however, patients with adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, or any other cancer from which the patient had been disease-free for more than 5 years were permitted. No severe acute or chronic medical condition that may have impaired the ability to participate in the study or interfered with the interpretation of results was permitted. Adverse events from prior anti-cancer therapy were to have recovered to grade ≤ 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 3.0) before randomisation. Patients were to have had no history of uncontrolled hypertension within 3 months before enrolment and no deep vein thrombosis within 4 weeks before randomisation. Patients were to have adequate organ and haematologic function. Pregnant and breast-feeding women were excluded. Patients of reproductive potential were required to use effective methods of contraception.

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table B4 presents the baseline characteristics of participants in Study EFC10262 (VELOUR). Patient characteristics and disease history (including prior anti-cancer treatments) were well balanced between the two treatment groups.

Table B4. **Baseline characteristics of all participants in Study EFC10262 (VELOUR)**

Study EFC10262 (VELOUR) Baseline characteristic	Aflibercept 4 mg/kg + FOLFIRI (n = 612)	Placebo + FOLFIRI (n = 614)
ECOG PS, n (%)		
0	349 (57.0)	350 (57.0)
1	250 (40.8)	250 (40.7)
2	13 (2.1)	14 (2.3)
Prior bevacizumab,[a] n (%)		
Yes	186 (30.4)	187 (30.5)
No	426 (69.6)	427 (69.5)
Sex, n (%)		
Male	365 (59.6)	353 (57.5)
Female	247 (40.4)	261 (42.5)
Age, years		
Median (range)	61.0 (21-82)	61.0 (19-86)
Age > 65 years, %	33.5	38.9
Caucasian/white race, n (%)	548 (89.5)	523 (85.2)
Primary site, n (%)		
Colon	289 (47.2)	302 (49.2)
Recto-sigmoid	123 (20.1)	136 (22.1)
Rectum	197 (32.2)	174 (28.3)
Other[b]	3 (0.5)	2 (0.3)
Median (range) time from first diagnosis to randomisation, months	14.62 (2.1-325.1)	13.67 (2.4-214.7)
Number of metastatic organs involved at baseline (excluding primary site), n (%)		
0	2 (0.3)	6 (1.0)
1	256 (41.8)	271 (44.1)
> 1	354 (57.8)	337 (54.9)
Metastatic organs involved at baseline (excluding primary site), n (%)		
Any site	610 (99.7)	608 (99.0)
Liver	459 (75.0)	431 (70.2)

Study EFC10262 (VELOUR) Baseline characteristic	Aflibercept 4 mg/kg + FOLFIRI (n = 612)	Placebo + FOLFIRI (n = 614)
Lung	271 (44.3)	277 (45.1)
Lymph nodes	173 (28.3)	181 (29.5)
Peritoneum	68 (11.1)	88 (14.3)
Liver metastasis, n (%)		
No liver metastasis, or liver and other metastases	459 (75.0)	468 (76.2)
Liver metastasis only	153 (25.0)	146 (23.8)
Prior chemotherapy, n (%)		
Adjuvant only[c]	60 (9.8)	64 (10.4)
Metastatic disease	450 (73.5)	442 (72.0)
Adjuvant and metastatic disease	102 (16.7)	108 (17.6)
Laboratory abnormalities at baseline		
Anaemia, %		
All grades	[redacted]	[redacted]
Grades 3-4	[redacted]	[redacted]
Elevated ALP, %		
All grades	[redacted]	[redacted]
Grades 3-4	[redacted]	[redacted]
Hypoalbuminaemia, %		
All grades	[redacted]	[redacted]
Grades 3-4	[redacted]	[redacted]
Elevated LDH (> ULN), %	[redacted]	[redacted]

ALP, alkaline phosphatase; ECOG PS, Eastern Cooperative Oncology Group performance status; CRC, colorectal cancer; FOLFIRI, fluorouracil/leucovorin/irinotecan; LDH, lactate dehydrogenase; SD, standard deviation; ULN, upper limit of normal.

[a] Prior bevacizumab status as provided at randomisation (stratification variable).

[b] Includes presumed colorectal primary, appendix, colon plus appendix, synchronous caecum, and rectum primary.

[c] Relapse within 6 months of completion of oxaliplatin-based adjuvant therapy.

Section 10.15.2 in appendix 15 presents baseline characteristics of subgroups included in the cost-effectiveness section. Patient characteristics and disease history (including prior anti-cancer treatments) were well balanced between the two treatment groups.

Outcomes

6.3.5 *Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as*

assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Table B5 presents the outcomes and assessments for Study EFC10262 (VELOUR).

Table B5. **Primary and secondary outcomes of Study EFC10262 (VELOUR)**

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
Study EFC10262 (VELOUR)	Overall survival (defined as the time interval from randomisation to death from any cause)	Overall survival is a recognised measure of clinical benefit and is used in clinical practice; it is a very reliable, unambiguous and objective endpoint, and is the most clinically meaningful endpoint in this setting	• Progression-free survival (defined as the interval from randomisation to the first observation of disease progression[a] (according to independent review committee review) or death from any cause) • Objective response (complete response and partial response [according to RECIST criteria version 1.0]) • Treatment-emergent adverse events and laboratory abnormalities	These endpoints are used in clinical practice

RECIST, Response Evaluation Criteria in Solid Tumors; VELOUR, Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Colorectal Cancer After Failure of an Oxaliplatin Based Regimen.

[a] Disease progression was determined by at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter since the treatment started, the unequivocal increase in the size of nontarget lesions, or the appearance of one or more new lesions. Hepatomegaly alone was not sufficient to assess progression. In the presence of evidence suggestive of progression, such as rising carcinoembryonic antigen (CEA), increasing liver enzymes, declining performance status, weight loss, or increasing pain, every reasonable effort was made to document the nature of progressive disease by appropriate imaging studies. The investigator could remove a patient from the study either for clinical progression, when it was not possible to obtain an imaging study, or for any other reason when it was determined that it was in the best interest of the patient to do so; the rationale for this decision was to be recorded.

Statistical analysis and definition of study groups

6.3.6 *State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.*

Table B6 presents information on the statistical analyses conducted in Study EFC10262 (VELOUR).

Table B6. **Summary of statistical analyses in Study EFC10262 (VELOUR)**

Trial no. (acronym)	Study EFC10262 (VELOUR)
Hypothesis objective	The primary objective of the VELOUR study was to evaluate the efficacy of the combination of aflibercept + FOLFIRI versus placebo + FOLFIRI in patients with mCRC, following disease progression while on or after completion of treatment with an oxaliplatin-based regimen.
Statistical analysis	• Efficacy analyses were conducted in the randomised population according to the arm assigned at randomisation; response rate was assessed in the subset of these patients who had measurable disease at baseline. • Time-to-event parameters were estimated using Kaplan-Meier analysis. Primary comparisons between treatment groups were performed using stratified log-rank tests with stratification factors specified at randomisation. • In pre-specified subgroup analyses, the consistency of the treatment effect on OS was evaluated with respect to stratification factors at randomisation (ECOG PS, prior bevacizumab) and a series of baseline characteristics: age, sex, location of primary tumour, number of organs with metastasis, liver metastasis, prior hypertension, and geographical region. The hazard ratio and confidence interval estimates in the primary and subgroup analyses were provided using a Cox proportional hazards model. • Response rate was compared between arms using a Cochran-Mantel-Haenszel test. • A test for interaction was performed for each subgroup analysis. For each parameter, a Cox proportional hazards model was used for the overall population, including the parameter, the treatment effect, and the treatment by parameter interaction, to evaluate any possible heterogeneity of the treatment effect among subgroups. Interactions between treatment and each subgroup were tested at the two-sided 10% level (i.e., a *P* value > 0.1). Within each subgroup, the treatment effect HR and its (1-α)% CIs were estimated using a Cox proportional hazards model on patients of this subgroup (Sanofi data on file, 2011). Safety was analysed in the treated population using descriptive methods, according to the treatment received (patients who received at least one dose of aflibercept were analysed in the aflibercept arm, regardless of treatment assignment).

Sample size, power calculation	• For the primary efficacy analysis (OS), it was determined that 863 events were required to detect, with 90% power, a 20% risk reduction in the aflibercept arm relative to the control arm, using a log-rank test at an overall two-sided significance level of 0.0499, taking into account stopping boundaries for two interim analyses. • Using a group sequential approach with an O'Brien Fleming α-spending function and an overall two-sided α level of 0.0499, the two-sided nominal significance level to be used at the final analysis of OS was 0.0466. • On the basis of an anticipated accrual over 30 months with 9 months follow-up, a total of 1,200 patients were required. • The cut-off date for OS was the date of the 863rd event (February 7, 2011).
Data management, patient withdrawals	Patients who discontinued treatment were followed for disease progression (imaging every 6 weeks) if discontinuation occurred prior to documented progression, and for survival status (every 2 months) once progressive disease was documented, until death or until the study cut-off date (whichever came first).
ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IRC, independent review committee; IVRS, interactive voice response system; FU, fluorouracil; mCRC, metastatic colorectal cancer; OS, overall survival.	

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post hoc.

In Study EFC10262 (VELOUR), a number of pre-specified subgroup analyses were performed to evaluate the consistency of the treatment effect on OS and PFS. Subgroup analyses were planned for the following baseline characteristics, stratification variables, and demographic characteristics:

Baseline Characteristics

- Presence of liver metastasis: yes; no
- Location of primary tumour: colon; rectosigmoid; rectum; other
- Number of metastatic organs: > 1; ≤ 1
- Prior history of hypertension: yes; no

Stratification Variables

- ECOG PS: 0; 1; 2
- Prior bevacizumab treatment: yes; no

Demographic Characteristics

- Age: < 65 years; ≥ 65 years
- Gender: male; female
- Race: white; other
- Geographical region: Western Europe; Eastern Europe; North America; South America; other region

Overall survival results (HR) for all pre-specified subgroups are shown in Figure B-8. Two subgroups are considered in more detail in this submission and are included in the economic analysis:

- Patients with liver metastases only
- Patients within the ITT population excluding those patients who relapsed on or within 6 months of adjuvant treatment

The pre-specified subgroup of patients with liver metastases only has been identified in previous NICE guidance as a recognised clinical subgroup in mCRC (NICE, 2010) and was chosen as a relevant subgroup for further exploration in this submission. These patients experienced a greater treatment effect on OS (unadjusted HR, 0.649 [95.34% CI, 0.492-0.855]; similar HR when adjusted for baseline value of performance status, prior bevacizumab, age, hypertension, number of metastatic organs, compared with patients with no liver metastases or liver and other organ involvement (unadjusted HR, 0.868 [95.34% CI, 0.742-1.015]; similar adjusted HR. A test for interaction by treatment was statistically significant at the 10% level (*P* = 0.0899). The liver metastases only subgroup was the only pre-specified subgroup that showed a significant interaction by treatment (see the forest plot in Figure B-8 in Section 6.5.3).

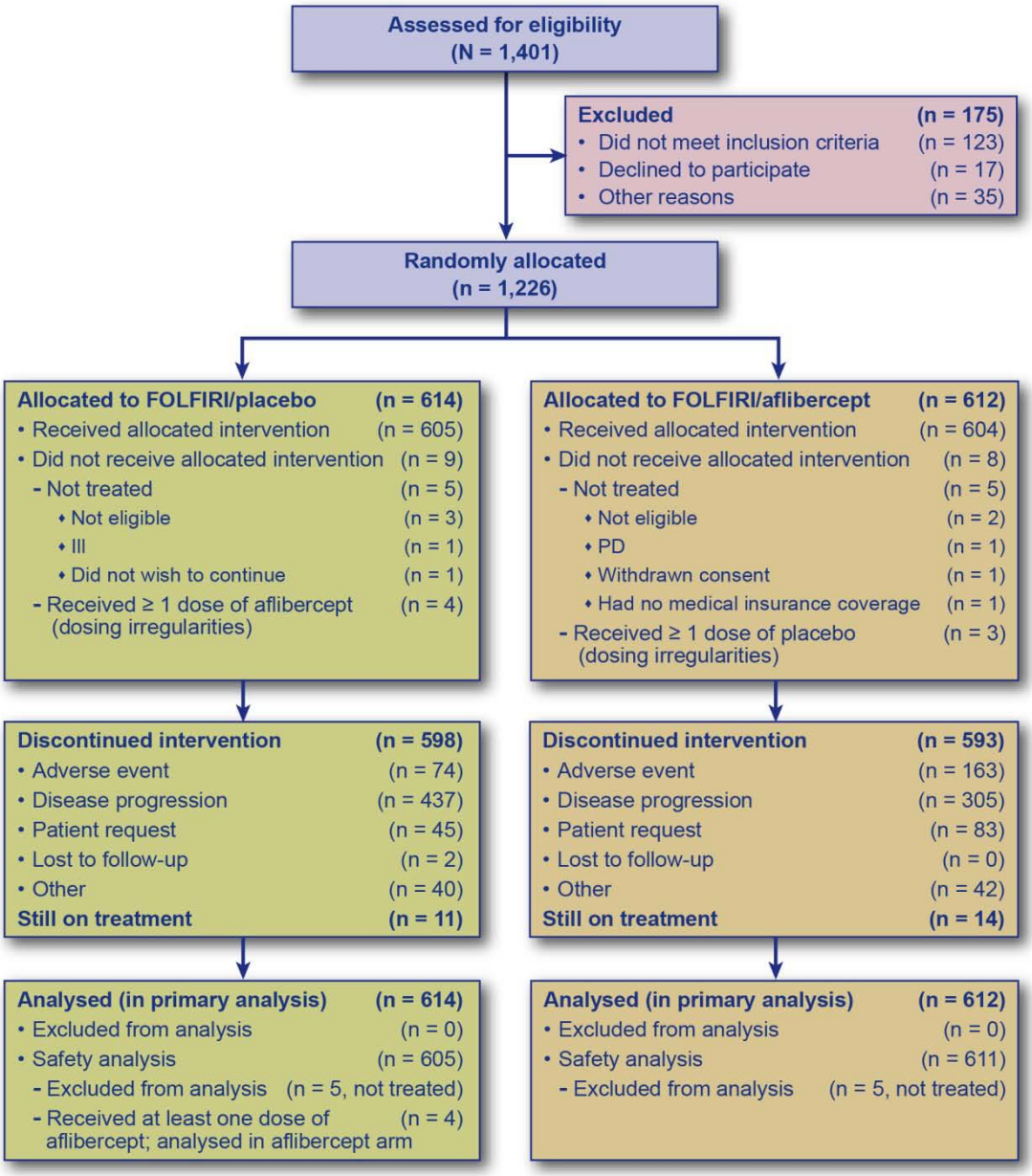
A second, post-hoc subgroup has been considered that consists of patients in the ITT population excluding those who received oxaliplatin as an adjuvant treatment. In the VELOUR study, 10% of included patients had relapsed during or within 6 months of completion of oxaliplatin-based adjuvant therapy, while the remainder had received oxaliplatin-based therapy for metastatic cancer. Rapid relapse after adjuvant therapy is typically associated with very aggressive disease and poor prognosis. This group of patients may have tumours with genetic changes that make them less sensitive to chemotherapy (Sargent et al., 2007). Therefore, this may represent a subset of patients who may not benefit from anti-VEGF/chemotherapy combination treatment, although the biological rationale for this is unclear. A post hoc analysis, also reported in the SmPC, was conducted on the subgroup of patients excluding these patients who relapsed during or within 6 months of completion of oxaliplatin-based adjuvant therapy. [redacted]

Participant flow

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

The CONSORT flow chart for VELOUR is provided in Figure B-2.

Figure B-2. **VELOUR CONSORT diagram of participant flow**



CONSORT, Consolidated Standards of Reporting Trials.

Source: Van Cutsem et al., 2012.

6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG.

Table B7 presents the quality assessment for VELOUR.

Table B7. **Quality assessment results for Study EFC10262 (VELOUR)**

Trial no. (acronym)	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Eligible patients were randomly assigned (1:1) using a centralised interactive voice response system based on a permuted-block randomisation, stratified according to prior therapy with bevacizumab (yes or no), and ECOG performance status (0, 1, or 2).	Yes
Was the concealment of treatment allocation adequate?	Aflibercept and placebo were supplied in indistinguishable sealed vials	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Patient characteristics and disease history (including prior anti-cancer treatments) were well balanced between the two treatment arms.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	VELOUR was a double-blind study. Response was assessed by a third party (independent review committee), blinded to patient treatment.	Yes
Were there any unexpected imbalances in drop-outs between groups?	The number of patients who discontinued treatment was 593 in the aflibercept + FOLFIRI group and 598 in the placebo + FOLFIRI group.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes noted in the methods were reported in the Van Cutsem et al., 2012 paper.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy analyses were conducted in the randomised population; response rate was assessed in the subset of these patients who had measurable disease at baseline.	Yes

ECOG, Eastern Cooperative Oncology Group; FOLFIRI, 5-fluorouracil plus folinic acid (or leucovorin) plus irinotecan; VELOUR, Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Colorectal Cancer After Failure of an Oxaliplatin Based Regimen.

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section appendix 3, for a suggested format.

Only the VELOUR study was identified; the full quality assessment for which is presented in Section 6.4.1.

6.4.3 *If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.*

6.5 ***Results of the relevant RCTs***

6.5.1 *Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.* ***If there is more than one RCT, tabulate the responses.***

6.5.2 *The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.*

6.5.3 *For each outcome for each included RCT.*

Efficacy Results from Study EFC10262 (VELOUR)

The efficacy results from study EFC10262 (VELOUR) for the OS, PFS, and response rates endpoints in all patients and by subgroup analysis are presented below.

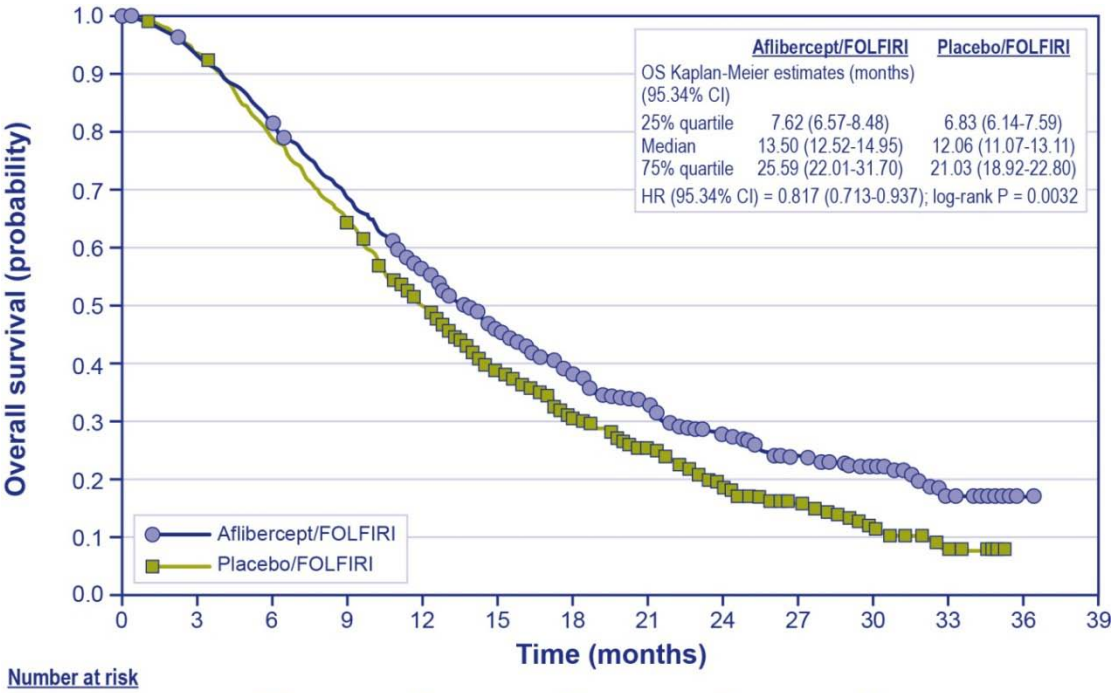
Results of the Analysis of the Primary Outcome

Overall survival

Analysis of OS in the ITT population was based on 863 death events, with 460 events (74.9%) reported in the placebo + FOLFIRI arm and 403 events (65.8%) in the aflibercept + FOLFIRI arm. At the final data cut-off date for survival analysis, the median follow-up time for the ITT population was 22.28 months.

Figure B-3 presents the Kaplan-Meier curves for OS by treatment group. There was a significant improvement in OS in the aflibercept + FOLFIRI group compared with the placebo + FOLFIRI group. The estimated HR was 0.817 (95.34% CI, 0.713-0.937; P = 0.0032), representing an 18.3% reduction in risk of death with aflibercept + FOLFIRI compared with placebo + FOLFIRI.

Figure B-3. **Kaplan-Meier estimates of overall survival for Study EFC10262 (VELOUR) (intention-to-treat population)**



Number at risk						
Aflibercept:	612	498	311	148	75	33
Placebo:	614	485	286	131	51	14
Survival probability (%)						
Aflibercept:		81.9	56.1	38.5	28.0	22.3
Placebo:		79.1	50.3	30.9	18.7	12.0

CI, confidence interval; FOLFIRI, fluorouracil/leucovorin/irinotecan; HR, hazard ratio; OS, overall survival.

Intention-to-treat patient population; cut-off date: 7 February 2011.

Source: Van Cutsem et al., 2012.

As shown in Figure B-4, the Kaplan-Meier curves for OS started to separate early and continued to separate, suggesting that there were patients who experienced a sustained benefit following treatment with aflibercept + FOLFIRI. The pronounced and sustained separation of the Kaplan-Meier curves presents a compelling argument that a median OS difference of 1.44 months may not fully reflect the overall clinical benefit of adding aflibercept to FOLFIRI.

The probabilities of surviving after 6, 12, 18, 24, and 30 months were higher in the aflibercept + FOLFIRI group than in the placebo + FOLFIRI group (Table B8 and Figure B-4). Overall survival probability at 2 years was 50% greater in patients treated with aflibercept + FOLFIRI compared with placebo + FOLFIRI and was 85% higher at 30 months.

Table B8. **Estimated survival probabilities by treatment group and time since diagnosis**

Time since diagnosis	Estimated survival probability (95.34% CI)	
	Aflibercept + FOLFIRI	Placebo + FOLFIRI
6 months	81.9% (78.8%-85.0%)	79.1% (75.9%-82.4%)

12 months	56.1% (52.1%-60.2%)	50.3% (46.2%-54.3%)
18 months	38.5% (34.3%-42.7%)	30.9% (26.9%-34.8%)
24 months	28.0% (23.7%-32.4%)	18.7% (14.9%-22.5%)
30 months	22.3% (17.8%-26.8%)	12.0% (8.0%-16.0%)
CI, confidence interval; FOLFIRI, fluorouracil/leucovorin/irinotecan		

A piecewise model calculating hazard ratios by 6-month periods shows improvement in the HR over time, consistent with the survival curves that continue to separate past the median time point, indicating that the magnitude of the aflibercept treatment effect continues to increase over time (Ruff 2013).

Table B9. **OS (Months), Piecewise Cox Model with Pre-defined Intervals (Per 6 Months) (ITT Population)**

Parameter	Time (months)	HR (95.34% CI) vs. Placebo + FOLFIRI
OS	t ≤ 6	0.860 (0.664-1.114)
OS	6 < t ≤ 12	0.838 (0.673-1.043)
OS	12 < t ≤ 18	0.782 (0.582-1.050)
OS	t > 18	0.676 (0.463-0.988)
CI, confidence interval; FOLFIRI, 5-fluorouracil plus folinic acid (or leucovorin) plus irinotecan; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival.		

Mean overall survival (post hoc analysis)

As discussed above, because of the continued separation of the survival curves over time, the median estimate does not provide a full picture of the survival benefit of aflibercept. The mean is likely to be a more helpful statistic because it takes into account the shape of the entire survival curve.

The mean OS observed in the VELOUR study could not be calculated directly from trial data because some patients were still alive at the end of study follow-up. Therefore, mean OS was estimated by fitting parametric functions to the trial data and extrapolating to provide complete curves (Joulain et al., 2012). The statistical analyses were performed in accordance with the NICE Decision Support Unit recommendations (Latimer, 2011.

Several standard parametric distributions were tested: exponential, Weibull, log-logistic, lognormal, and Gompertz (Joulain et al., 2012). Evaluation of fit was performed using diagnostic plots (e.g., log cumulative hazard plots), Akaike information criterion (AIC) and Bayesian information criterion (BIC) tests, visual inspection of fit to the Kaplan-Meier data, and consideration of the biological and clinical plausibility of the extrapolation beyond the end of trial follow-up. Because the OS curves were quite close to being complete, especially in the placebo arm, evaluation of fit may be heavily guided by the AIC and BIC results and the plots.

The AIC and BIC test results for the ITT population are presented in Table B10; visual inspection plots are presented in Figure B-4, and Figure B-5.

Table B10. **AIC and BIC test results for OS functions, ITT population**

Function	Aflibercept + FOLFIRI		Placebo + FOLFIRI		Both arms (proportional hazards)	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	1497.06	1505.89	1469.34	1478.18	2967.33	2982.67
Log-normal	1491.14	1499.98	1469.08	1477.92	2965.32	2980.66
Log-logistic	1479.70	1488.53	1457.19	1466.03	2939.84	2955.17
Exponential	1535.40	1539.82	1549.73	1554.15	3085.14	3095.36
Gompertz	1524.47	1533.30	1510.60	1519.44	3037.04	3052.38

Values in red font indicate the lowest AIC and BIC values.

AIC, Akaike information criterion; BIC, Bayesian information criterion; FOLFIRI, fluorouracil/leucovorin/irinotecan; ITT, intention-to-treat; OS, overall survival.

Source: Joulain et al. 2012

[redacted]

[redacted]

FOLFIRI, fluorouracil/leucovorin/irinotecan; ITT, intention-to-treat; KM, Kaplan-Meier; OS, overall survival. (6 months = 13 cycles, 12 months – 26 cycles, 2 yrs = 52 cycles)

The log-cumulative hazard plots demonstrated mild non-proportionality (reported in the Clinical Study Report) - the curves for the two treatment arms were non-parallel and crossed over one another (Figure B-6). Because of the need to extrapolate beyond the duration of the study follow-up, this non-proportionality was considered important to take into account, and so the treatment arms were modelled separately, rather than modelling treatment as a covariate.

Figure B-6. **Log–cumulative hazard plots for overall survival for ITT population**

[redacted]

ITT, intention-to-treat.

Functions fitted to each treatment arm separately are described further as follows:

- For the aflibercept + FOLFIRI arm, the lowest AIC and BIC results were obtained for the log-logistic function, followed by the log-normal, Weibull, and exponential functions. On visual inspection, the log-logistic function followed the Kaplan-Meier data more closely than the Weibull or log-normal functions.
- For the placebo + FOLFIRI arm, the lowest AIC and BIC results were obtained for the log-logistic function, followed by the log-normal and Weibull functions (which gave similar results) and the exponential function. On visual inspection, the log-logistic and the log-normal functions overestimated OS at the end of the Kaplan-Meier data, while the Weibull function underestimated OS at the same point.
- At the end of trial follow-up, the log-logistic function predicted a slightly smaller difference in OS between treatment groups than the Weibull function. The log-logistic functions coincided with the Kaplan-Meier estimates for A-FOLFIRI and overestimated OS compared with the Kaplan-Meier estimates for FOLFIRI.

Therefore, the log-logistic function appeared to provide the best overall fit for OS for the two treatment groups; these functions were selected as the base-case for the economic analysis (other functions were explored in sensitivity analysis).

The log-logistic and log-normal functions have a longer tail than the commonly used Weibull function, indicating that a small percentage of patients will have a relatively long survival. This observation has been reported for many cancers, including those of the liver, cervix, uterus, mouth, throat, rectum, and breast (Muszbek, 2012, Boag et al., 1949; Chapman et al., 1992, 2006; McCready et al., 2000; Royston, 2001). Previous studies have shown long-term survival for approximately 8% to 10% of patients with mCRC without surgery (Kopetz et al.,

2009; Sanoff et al., 2008). For example, a retrospective review of patients newly diagnosed with mCRC treated between 1990 and 2006, reported that the 5-year survival of patients who did not undergo liver resection was 19.5%, although median OS was only 26.7 months (Kopetz et al., 2009). This supports the clinical plausibility of the log-logistic function in modelling OS with aflibercept.

Because of the longer tail of the log-logistic function, the curves were truncated at 15 years to avoid implausibly long survival times (Joulain et al., 2012). This gave an estimate of improvement in mean OS of 4.7 months for aflibercept + FOLFIRI compared with placebo + FOLFIRI (Joulain et al., 2012). Without truncation of the curves, the estimate was 6.6 months (Joulain et al., 2012). For the other functions tested, differences in truncated mean OS ranged from 3.0 [redacted] months (Table B11).

Table B11. **Estimated mean overall survival at 15 years for the ITT population**

	Mean overall survival at 15 years (months)		
	Aflibercept + FOLFIRI	**Placebo + FOLFIRI**	**Difference**
Log-logistic distribution (by treatment separately[a])	**22.8**	**18.1**	**4.7**
Weibull distribution (by treatment separately)	17.9	14.9	3.0
Log-normal distribution (by treatment separately)	[redacted]	[redacted]	[redacted]
Exponential distribution **(**by treatment separately**)**	[redacted]	[redacted]	[redacted]

FOLFIRI, fluorouracil/leucovorin/irinotecan; ITT, intention-to-treat.

[a] Function providing best fit.

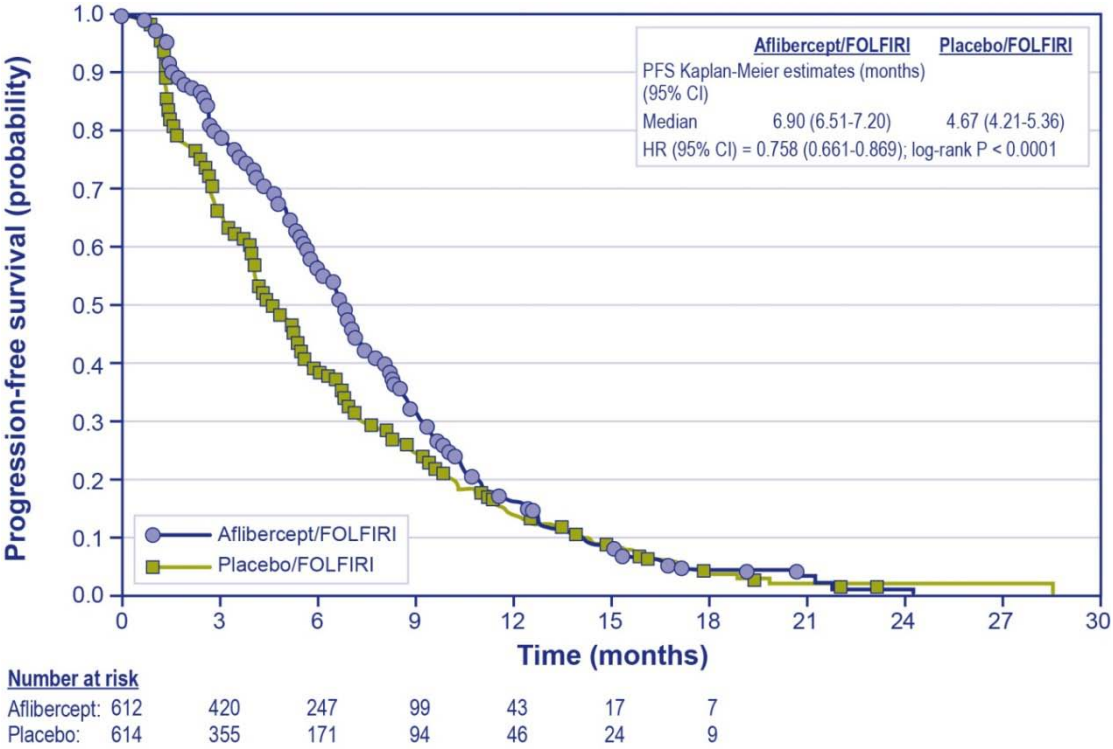
See Appendix 14 for 'treatment as covariate' analyses.

Results of the Analyses of the Secondary Outcomes

Progression-free survival

Addition of aflibercept to FOLFIRI also increased PFS relative to placebo plus FOLFIRI. The median PFS gain was 2.23 months – 6.90 [95% CI 6.51 – 7.20) months for aflibercept plus FOLFIRI versus 4.67 [95% CI: 4.21 – 5.36) for placebo plus FOLFIRI, based on independent assessment of radiologic progression. The HR was 0.758 (95% CI: 0.661 – 0.869) (Figure B-7).

Figure B-7. **Kaplan-Meier estimates of progression-free survival for Study EFC10262 (VELOUR) (intention-to-treat population)**



CI, confidence interval; FOLFIRI, fluorouracil/leucovorin/irinotecan; HR, hazard ratio; ITT, intention to treat; PFS, progression-free survival.

Intention-to-treat population; cut-off date: 6 May 2010.

Source: Van Cutsem et al., 2012; Sanofi data on file, 2011.

For 42 patients (26 aflibercept + FOLFIRI, 16 placebo + FOLFIRI) who died prior to the implementation of the IRC review or who refused consent for this review, the investigator's tumour assessment was used (Sanofi data on file, 2011).

Response rate

Evaluation of tumour response rate (complete response + partial response) in the evaluable population was based on assessment performed by the IRC and was conducted in 530 patients in the placebo + FOLFIRI arm and 531 patients in the aflibercept + FOLFIRI arm. Aflibercept + FOLFIRI significantly improved the response rate when compared with placebo + FOLFIRI. The response rate was 19.8% (95% CI, 16.4 to 23.2) in the aflibercept + FOLFIRI arm versus 11.1% in the FOLFIRI plus placebo arm (Table B12).

Table B12. **Response rates for the VELOUR study: evaluable population**

Response rates (secondary endpoint, evaluable population)	Aflibercept 4 mg/kg + FOLFIRI (n = 612)	Placebo + FOLFIRI (n = 614)	*P* value
Evaluable population, n	531	530	
Response rate (complete or partial response), n (%) [95% CI, %]	105 (19.8) [16.4-23.2]	59 (11.1) [8.5-13.8]	< 0.001
Complete response, n (%)	0	2 (0.4)	—
Partial response, n (%)	105 (19.8)	57 (10.8)	—
Stable disease, n (%)	350 (65.9)	344 (64.9)	—
Progressive disease, n (%)	55 (10.4)	114 (21.5)	—
Not evaluable, n (%)	21 (4.0)	13 (2.5)	

CI, confidence interval; FOLFIRI, fluorouracil/leucovorin/irinotecan.

The evaluable population included all randomised patients with measurable disease at study entry, with at least one valid post-baseline tumour evaluation, and who gave consent for third-party review.

Source: Van Cutsem et al., 2012.

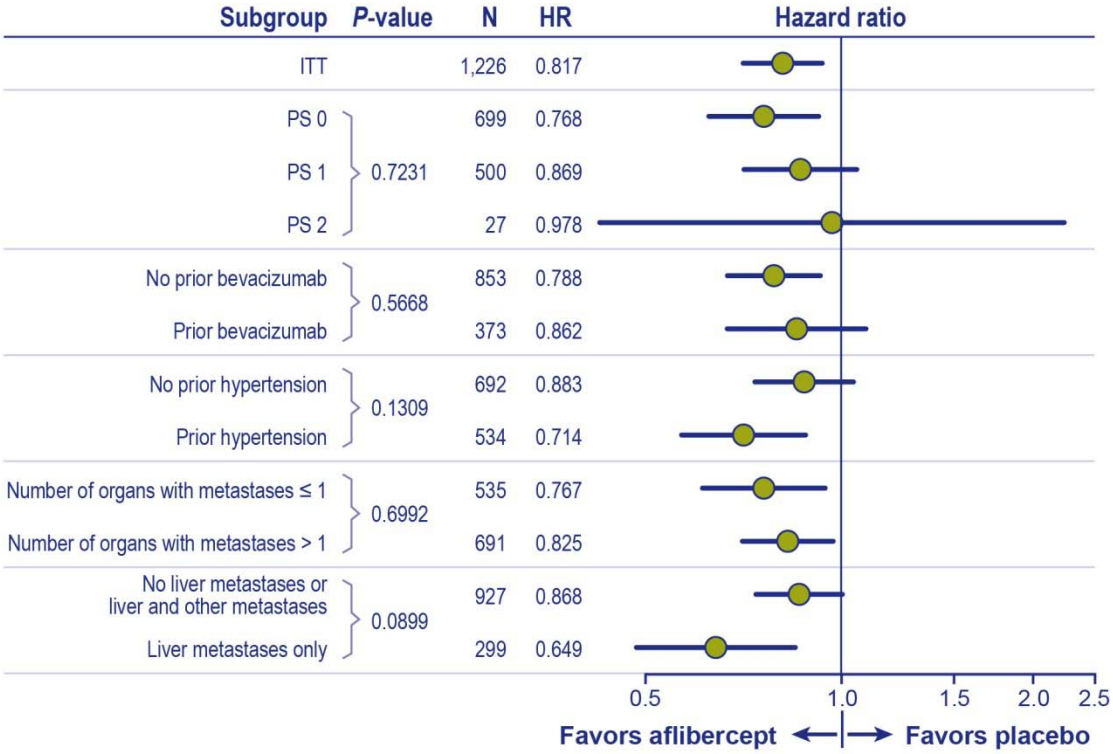
Subgroup Analyses Results

Analysis of overall survival based on pre-specified subgroups

In the pre-specified subgroup analyses, there was no evidence of interaction between treatment groups and stratification factors or demographic characteristics (including prior bevacizumab status) (Figure B-8), indicating an overall consistent treatment effect across those subgroups.

As described in section 6.5.3, of the baseline characteristics, only the pre-specified subgroup of patients with liver metastases showed a greater OS benefit, and a test for interaction was significant at the 10% level (*P* = 0.0899) (Figure B-8). Median OS in this group was [redacted] HR, 0.649 (95.34% CI, 0.492-0.855).

Figure B-8. **Overall survival for Study EFC10262 (VELOUR) (ITT population) by prespecified subgroups (prognostic, prior treatment, and performance status)**



HR, hazard ratio; ITT, intention-to-treat; PS, performance status; VELOUR, Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Colorectal Cancer After Failure of an Oxaliplatin Based Regimen.

Source: Sanofi data on file, 2013.

A post hoc analysis of a subgroup excluding patients who relapsed on or within 6 months of adjuvant treatment was also conducted. This subgroup comprised 1,102 patients (aflibercept + FOLFIRI, n = 552; placebo + FOLFIRI, n = 550). A greater treatment effect was observed in this patient group (aflibercept + FOLFIRI vs. placebo + FOLFIRI: 13.8 months [95% CI, 12.68-15.44 months] vs. 11.9 months [95% CI, 10.88-13.01 months]; unadjusted HR, 0.78 [95% CI, 0.68-0.90]; adjusted HR, 0.80 [95%CI, 0.692-0.919]) compared with those patients who received adjuvant only treatment (unadjusted HR, 1.092 [95%CI, 0.704-1.694]; adjusted HR, 1.047 [95% CI, 0.664-1.649]; *P* value for interaction with treatment = 0.1265).

Analysis of progression-free survival based on pre-specified subgroups

As with the OS subgroup analysis, pre-specified subgroup analysis of PFS showed no significant interaction between treatment arms and stratification factors or demographic factors, demonstrating a consistent treatment effect across these subgroups.

Consistent with subgroup analysis of OS, subgroup analysis of PFS based on patients' baseline disease characteristics showed a significant interaction at the 10% level between treatment arms and the liver metastasis subgroups, demonstrating a greater effect of treatment in patients with liver metastases only

[redacted] compared with those patients with no liver metastasis or liver metastasis with other metastases [redacted] Details of estimation of mean PFS are provided in section 7.9.3.

A post hoc analysis of a subgroup of patients excluding those who relapsed within 6 months of adjuvant treatment was conducted. The PFS benefit in this group was [redacted] compared with those patients who only received adjuvant treatment [redacted]

Details of estimation of mean PFS are provided in section 7.9.3.

6.6 Meta-analysis

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

No meta-analysis was undertaken as only one study of aflibercept in second-line mCRC was identified in the systematic review.

Of the 30 studies identified in the systematic review, six assessed the FOLFIRI regimen—Galal et al., 2008; Muro et al., 2010; Peeters et al., 2010; Peeters et al., 2011; Van Cutsem et al., 2012; Clarke et al., 2011 (Table B13; see Appendix 2, section 10.2.8 for general characteristics of these studies).

The dose and schedule of the FOLFIRI regimen was not reported in one study (Peeters et al., 2011). The comparability of the FOLFIRI dose and administration schedules among the remaining five studies was investigated. The doses and schedules appeared to be similar among the five studies, although the VELOUR study included placebo along with FOLFIRI administration (Van Cutsem et al., 2012). Two studies (Peeters et al., 2010; Peeters et al., 2011) did not report the duration of treatment.

Table B13. **Treatment details: FOLFIRI regimen**

Trial Name, Author	Agent[a] and Dose	Route of Administration	Length per Cycle	Median (range) Cycles or Treatment Duration
DaVINCI, Clarke 2011	• Irinotecan 180 mg/m^2 • 5-FU 400 mg/m^2 • 5-FU 2,400 mg/m^2 • FA 20 mg/m^2	• 90-minute infusion, day 1 • IV bolus, day 1 • 46-hour infusion • IV bolus	2 weeks	4.4 months
FIRIS, Muro 2010	• FA 200 mg/m^2 • Irinotecan 150 mg/m^2 • FU 400 mg/m^2 • FU 2,400 mg/m^2	• Day 1 • Day 1 • Bolus, day 1 • 46-hour infusion	2 weeks	4.7 cycles (1–20)
Galal 2008[b]	• Irinotecan 180 mg/m^2 • FA 400 mg/m^2 • 5-FU 400 mg/m^2 IV bolus • 5-FU 2,400 mg/m^2 IV	• 90-minute IV, day 1 • 120-minute IV, day 1 • IV bolus, day 1 • 46-hour infusion, day 1	2 weeks	6 cycles
Peeters 2010	• Irinotecan 180 mg/m^2 • Racemic FA 400 mg/m^2 (or *l*-FA 200 mg/m^2) • FU 400 mg/m^2 • FU 2,400 mg/m^2	• Day 1 • Day 1 • Bolus, day 1 • 1–2 infusions	2 weeks	NR
Peeters 2011	• FOLFIRI regimen NR	• IV infusion	2 weeks	NR
VELOUR, Van Cutsem 2012	• Irinotecan 180 mg/m^2 • FA 400 mg/m^2 • 5-FU 400 mg/m^2 • 5-FU 2,400 mg/m^2	• 90-minute IV day 1 • 120-minute IV day 1 • IV bolus, day 1 • 46-hour continuous infusion, day 1	2 weeks	8–9 cycles

5-FU = 5-fluorouracil; FA = folinic acid (leucovorin/folic acid); FOLFIRI, fluorouracil/leucovorin/irinotecan; FU = fluorouracil; IV = intravenous; NR = not reported; [a] Folinic acid (INN) and leucovorin (USAN) are synonyms for folic acid (FA) that will be preferentially used throughout the report. [b] Patients receiving first-line oxaliplatin-based regimens received fluoropyrimidine + irinotecan (± bevacizumab) regimens as second-line regimens and patients receiving first-line irinotecan-based regimens received fluoropyrimidine + oxaliplatin (± bevacizumab) regimens as second-line regimens in trial.

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable.

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

Not applicable.

6.7 Indirect and mixed treatment comparisons

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in appendix 4.

A systematic literature review was undertaken to identify studies evaluating second-line treatment of mCRC. The strategy used for searching is described in section 6.1.

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in appendix 5, a complete quality assessment for each comparator RCT identified.

The study selection criteria are described in section 6.2.1, and a flow diagram describing the number of studies included or excluded is shown in section 6.2.2.

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

A head-to-head trial has been conducted comparing aflibercept + FOLFIRI with the single relevant comparator, Placebo + FOLFIRI. As such, an indirect comparison was not conducted.

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

As explained in section 6.7.3, an indirect comparison was not conducted.

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

As explained in section 6.7.3, an indirect comparison was not conducted.

6.7.6 Please present the results of the analysis.

As explained in section 6.7.3, an indirect comparison was not conducted.

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

As explained in section 6.7.3, an indirect comparison was not conducted.

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

As explained in section 6.7.3, an indirect comparison was not conducted.

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

As explained in section 6.7.3, an indirect comparison was not conducted.

6.8 Non-RCT evidence

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in appendices 6 and 7.

Section 6.2.7 describes the AFLIBC06097 non-RCT study (ASQoP), which is investigating the safety and health-related quality of life (HRQL) of aflibercept in patients with mCRC.

The ASQoP trial is an international, prospective multicentre, single-arm, open-label phase 3b/4 study.

The primary objective of this study is to evaluate the safety of aflibercept in patients with mCRC treated with FOLFIRI after failure of an oxaliplatin-based regimen. Patients in this study are similar to those evaluated in the VELOUR trial. The secondary objective of the ASQoP study is to document the health-related quality of life (HRQL) in this patient population and capture those utility values not collected during the conduct of the VELOUR study. The primary and secondary endpoints of the study are listed in Table A-2. The total expected number of patients globally is 900, and 50 of these patients are expected to be enrolled in the UK.

[redacted]

[redacted]

	Number of Patients
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
HRQL, health-related quality of life; SD, standard deviation.	

Sections 7.4.5 and 7.4.6 provide details of the study results. Further data from this study should become available during the course of the appraisal process.

An additional utility study conducted in the UK and the Netherlands has also been identified (known as the mCRC utilities study); results are provided in Sections 7.4.5 and 7.4.6. The values from this study are included in the model.

6.9 Adverse events

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in appendices 8 and 9.

One ongoing single-arm Phase 3 study is investigating the safety of aflibercept in patients with mCRC – the ASQoP study (AFLIBC06097 - described in Table A-2, section 6.2.7, and section 6.8.1).Interim results are provided in section 6.8.1.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

The safety of aflibercept + FOLFIRI has been compared with placebo + FOLFIRI in the VELOUR study (Van Cutsem et al., 2012).

Treatment-emergent adverse events were reported in 99.2% and 97.9% of the aflibercept arm and control arm patients, respectively, with grade 3 and 4 events reported in 83.5% and 62.5% of patients, respectively. Table B15 summarises the incidence of the most frequently reported adverse events at all grades and at grades 3 and 4, including also the incidence of events that may be typically associated with anti-VEGF therapy.

A higher incidence of grade 3 and 4 adverse events was reported in the aflibercept arm compared with the control arm for hypertension, haemorrhage (2.9% vs. 1.7%), arterial thromboembolic events (1.8% vs. 0.5%), and venous thromboembolic events (7.9% vs. 6.3%). With respect to the grade 3 and 4 hypertension, 19.1% of patients in the aflibercept arm and 1.5% of patients in the control arm developed grade 3 hypertension (i.e., requiring adjustment in existing anti-hypertensive therapy or treatment with more than one drug); only one patient in the aflibercept arm (0.2%) experienced grade 4 hypertension.

The incidence of grade 3 or 4 gastrointestinal fistula, other fistulae, and gastrointestinal perforation was less than 2% in both treatment groups; acute grade 3 and 4 drug reactions were reported in 0.5% of patients in both arms. Grade 3 or 4 proteinuria was reported in 7.9% of patients in the aflibercept arm (including two patients with nephritic syndrome) and 1.2% of patients in the control arm.

Some adverse events commonly associated with chemotherapy were reported at a higher incidence in the aflibercept arm, including the following grade 3 and 4 events: diarrhoea (19.3% vs. 7.8%), asthenic conditions (16.9% vs. 10.6%), stomatitis and ulceration (13.7% vs. 5.0%), infections (12.3% vs. 6.9%), and palmar-plantar erythrodysesthesia (2.8% vs. 0.5%). Grade 3 and 4 neutropaenia (36.7% vs. 29.5%) and thrombocytopaenia (3.3% vs. 1.7%) were more common with aflibercept treatment, as was grade 3 and 4 complicated neutropaenia (5.7% vs. 2.8%).

Adverse events led to permanent discontinuation from study treatment in 26.8% of patients in the aflibercept arm and 12.1% of patients in the control arm. The adverse events (all grades) leading most frequently to permanent discontinuation of study treatment were asthenic conditions (3.8% vs. 1.3%, respectively), infections (3.4% vs. 1.7%), diarrhoea (2.3% vs. 0.7%), and hypertension (2.3% vs. 0%).

The majority of grade 3-4 adverse events occurred during early treatment cycles. Toxicities observed in VELOUR did not lead to a reduced cumulative exposure to chemotherapy (Van Cutsem 2011) and did not preclude patients from receiving further systemic anti-cancer treatment.

Table B15. **VELOUR: most frequent adverse events (incidence ≥ 20% or ≥ 5% higher in aflibercept arm), other anti-VEGF–associated events, and most frequent biologic abnormalities: safety population**

Adverse event[a]	Aflibercept + FOLFIRI (n = 611)			Placebo + FOLFIRI (n = 605)		
	All grades (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade 3 (%)	Grade 4 (%)
Any	99.2	62.0	21.4	97.9	45.1	17.4
Diarrhoea (PT)	69.2	19.0	0.3	56.5	7.6	0.2
Asthenic conditions (HLT)	60.4	16.0	0.8	50.2	10.4	0.2
Stomatitis and ulceration (LT)	54.8	13.6	0.2	34.9	5.0	—
Nausea (PT)	53.4	1.8	—	54.0	3.0	—
Infections and infestations (SOC)	46.2	11.0	1.3	32.7	6.1	0.8
Hypertension	41.4	19.1	0.2	10.7	1.5	—
Haemorrhage	37.8	2.8	0.2	19.0	1.7	—
Epistaxis	27.7	0.2	—	7.4	—	—
GI and abdominal pains (HLT)	34.0	5.1	0.3	29.1	3.1	0.2
Vomiting (PT)	32.9	2.6	0.2	33.4	3.5	—
Decreased appetite (PT)	31.9	3.4	—	23.8	1.7	0.2
Weight decreased	31.9	2.6	—	14.4	0.8	—
Alopecia (PT)	26.8	—	—	30.1	—	—
Dysphonia (PT)	25.4	0.5	—	3.3	—	—
Constipation (PT)	22.4	0.8	—	24.6	1.0	—
Headache (PT)	22.3	1.6	—	8.8	0.3	—
Palmar-plantar erythrodysesthesia syndrome	11.0	2.8	—	4.3	0.5	—

Adverse event[a]	Aflibercept + FOLFIRI (n = 611)			Placebo + FOLFIRI (n = 605)		
	All grades (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade 3 (%)	Grade 4 (%)
Other anti-VEGF–associated events						
Arterial thromboembolic events	2.6	0.8	1.0	1.5	0.5	—
Venous thromboembolic events	9.3	3.1	4.7	7.3	2.6	3.6
Fistula from GI origin	1.1	0.3	—	0.3	0.2	—
Fistula from other than GI origin	0.3	—	—	0.2	—	—
GI perforation	0.5	0.2	0.3	0.5	0.2	0.2
Biologic abnormalities						
Haematologic						
Anaemia	82.3	3.3	0.5	91.1	3.5	0.8
Neutropaenia	67.8	23.1	13.6	56.3	19.1	10.4
Neutropaenic complications	6.5	4.4	1.3	3.0	1.7	1.2
Thrombocytopaenia	47.7	1.7	1.7	33.8	0.8	0.8
Non-haematologic						
Proteinuria	62.2	7.5	0.3	40.7	1.2	—
ALT increased	47.3	2.5	0.2	37.1	2.2	—

ALT, alanine aminotransferase; FOLFIRI, fluorouracil/leucovorin/irinotecan; GI, gastrointestinal; HLT, high-level term; PT, preferred term; SOC, system organ class; VEGF, vascular endothelial growth factor.

[a] Grades were determined according to the National Cancer Institute Common Terminology Criteria of Adverse Events, version 3.0.

Source: Van Cutsem et al., 2012.

Meta-analysis of aflibercept adverse events

A meta-analysis was performed on pooled safety data from the locked databases of the following three phase 3 studies of aflibercept, which have been completed and reported:

- VELOUR: involving patients with mCRC (Van Cutsem et al., 2012)
- VITAL: involving patients with non-small cell lung cancer (Novello et al., 2011)
- VANILLA: involving patients with metastatic pancreatic cancer (Riess et al., 2010)

- Safety data from 2,662 patients (aflibercept, 1,333; placebo, 1,329) were included in the meta-analysis (Allegra et al., 2012; Tabernero et al., 2012).
    - Full details are provided in appendix 8.
    - Among patients treated with aflibercept, 0.4% and 0.5% experienced grade 4 hypertension and nephrotic syndrome, respectively (Allegra et al., 2012; Tabernero et al., 2012). The addition of aflibercept to concurrent chemotherapies did not increase the risk of venous thromboembolism. The risk of grade 3-4 anti-VEGF class adverse events was increased when adding aflibercept to concurrent chemotherapies (Allegra et al., 2012; Tabernero et al., 2012). This increased risk was statistically significant only for hypertension (RR, 9.21; 95% CI, 5.91-14.36), proteinuria (RR, 8.37; 95% CI, 4.37-16.06), and haemorrhage (RR, 2.04; 95% CI, 1.20-3.47). Other adverse events of interest that occurred with insufficient frequency to be included in this meta-analysis included the following:
    - One case of reversible posterior leukoencephalopathy syndrome in one patient who received placebo in the VANILLA study
    - Three cases of thrombotic microangiopathy in the VITAL and VELOUR studies (2 in VITAL, 1 in VELOUR; all in the aflibercept arm).

Some adverse events typically associated with backbone chemotherapies used in the three clinical trials were increased with the addition of aflibercept. In the VELOUR study, these adverse events included neutropaenia, neutropenic complications, stomatitis, diarrhoea, dehydration, and palmar plantar erythrodysaesthesia syndrome (hand foot syndrome) (Allegra et al., 2012; Tabernero et al., 2012).

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

In the VELOUR study, aflibercept + FOLFIRI demonstrated a positive risk-benefit balance for patients with mCRC with progressive disease following treatment with an oxaliplatin-based therapy (EMA/CHMP Zaltrap Summary of Opinion, 2012).

The safety profile of aflibercept + FOLFIRI in the VELOUR study indicated that adverse events were generally reversible and manageable using current clinical practice. There were two main types of AEs observed: (1) those normally associated with FOLFIRI/irinotecan chemotherapy, which occurred at a higher rate in the aflibercept arm but for which clinicians in the UK will be used to monitoring and managing; and (2) AEs typical of anti-angiogenic therapies in general. No unexpected AEs were observed.

The incidence of adverse events, including grade 3-4 adverse events, was increased in the aflibercept arm. However, the incidence of grade 4 adverse events was similar between treatment arms (overall incidence of any grade 4 adverse event: aflibercept + FOLFIRI, 21.4%; placebo + FOLFIRI, 17.4%).

The majority of grade 3-4 adverse events occurred during early treatment cycles. Further mitigation of the risk of AEs could be achieved by early monitoring and implementation of appropriate management strategies. Toxicities observed in VELOUR did not lead to a reduced cumulative exposure to chemotherapy (Van Cutsem 2011) and did not preclude patients from receiving further systemic anti-cancer treatment.

6.10 Interpretation of clinical evidence

6.10.1 *Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology*.

The efficacy and safety of aflibercept plus FOLFIRI in patients with mCRC previously treated with an oxaliplatin-based regimen has been demonstrated in a large, multinational RCT (VELOUR).

Aflibercept demonstrated meaningful and significant improvements in the primary and the two key secondary outcome measures:

- **Aflibercept significantly improved overall survival (primary endpoint):**
  - Median OS was increased by 1.44 months in the aflibercept + FOLFIRI group compared with placebo + FOLFIRI (13.50 months vs. 12.06 months, respectively; HR, 0.817; 95.34% CI, 0.713-0.937; P = 0.0032).
  - Survival curves diverged early and continued to diverge beyond the median. This is reflected in the comparative survival rates at different timepoints. At 24 months, 50% more patients were alive in the aflibercept arm - 28.0% in the aflibercept arm versus 18.7% in the FOLFIRI arm. At 30 months, 22.3% were alive in the aflibercept arm

versus 12.0% in the FOLFIRI arm (an 85% increase). This continued separation of the Kaplan-Meier curves is consistent with a sustained benefit of treatment experienced by some patients.

– Mean OS was increased by an estimated 4.7 months, representing an increase of over 25% in the expected survival duration (according to the log-logistic function which provided the best statistical and visual fit).

- **Aflibercept significantly improved progression-free survival:**

– Median PFS was increased by 2.23 months in the aflibercept + FOLFIRI group compared with placebo + FOLFIRI (HR, 0.758; 95% CI, 0.661-0.869; $P < 0.0001$).

- **Aflibercept produced significantly higher overall response rates:**

– The ORR was 19.8% (95% CI, 16.4-23.2) in the aflibercept + FOLFIRI arm compared with 11.1% (95% CI, 8.5-13.8) in the placebo + FOLFIRI arm ($P < 0.001$).

The safety profile of aflibercept was clinically manageable using current practice and as expected based on the safety profile of existing anti-VEGF therapies:

- There were two main types of AEs; those typical of the FOLFIRI regimen and which are managed routinely by oncologists treating CRC (the incidences of which were increased in the aflibercept arm), and those typical of anti-angiogenic agents as a class.
- Adding aflibercept increased the specific chemotherapy-related toxicity, particularly in terms of grade 3 and 4 events, including neutropaenia (36.7% vs. 29.5%), diarrhoea (19.3% vs. 7.8%), asthenia (16.9% vs. 10.6%), and stomatitis and ulceration (13.7% vs. 5.0%).
- The majority of grade 3 – 4 events occurred during early treatment cycles and many common AEs occurred only once (Van Cutsem 2011).

The CHMP concluded that there was a positive risk-benefit balance for aflibercept (EMA/CHMP Zaltrap Summary of Opinion, 2012).

Aflibercept is the only treatment to demonstrate a survival benefit in combination with FOLFIRI in patients previously treated with an oxaliplatin-containing regimen compared with patients treated with FOLFIRI alone.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths

The primary efficacy and safety evidence for aflibercept is based on a large, international, randomised, controlled trial (VELOUR; N = 1,226). Patients, investigators, and other persons responsible for study conduct and data analyses remained blinded to the study treatment assignment.

In VELOUR, aflibercept in combination with FOLFIRI was compared against FOLFIRI alone. FOLFIRI is standard of care second-line therapy within the NHS, and this position is reflective of NICE guidance – CG131 recommends oxaliplatin-based combination chemotherapy (e.g., FOLFOX) for first-line treatment of metastatic disease followed by irinotecan-based regimens (FOLFIRI or irinotecan monotherapy) as second-line therapy (unless contraindicated).

The efficacy of aflibercept + FOLFIRI has been demonstrated versus placebo + FOLFIRI using endpoints that are directly relevant to the clinical benefits experienced by patients in practice (i.e., OS, PFS, and overall response). Statistically significant and clinically meaningful improvements were observed consistently in OS, PFS, and ORR.

Limitations

The available evidence on aflibercept efficacy does not capture survival data for all patients. Those remaining alive beyond the end of the study follow-up will not contribute to our estimate of OS.

Patients entering the VELOUR trial were required to receive full dose FOLFIRI as defined in the protocol. However, in current practice, it is typical in the second-line setting (and in some other trials) for patients to receive less intense regimens in the second-line setting, as clinicians adjust dosing to the patient's individual circumstances, perhaps to accommodate or mitigate toxicities experienced under first-line treatment. Therefore, higher toxicity may have been observed in the VELOUR study (on both treatment arms) than may otherwise be experienced in the usual clinic setting.

Health-related quality of life data were not collected in VELOUR. To remedy this, the ASQoP trial is collecting HRQL data. Furthermore, an observational study in mCRC (the mCRC utilities study) was conducted to estimate the utility of patients on and following second-line therapy.

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

The clinical evidence base is relevant to the decision problem. The VELOUR trial reports on the relevant outcomes specified in the decision problem and compares the new intervention to the main comparator described in the scope.

6.10.4 *Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?*

Aflibercept dose and frequency in the VELOUR trial

In the VELOUR trial, aflibercept was administered at the same dose and frequency as the licensed dose that will be used in clinical practice (4 mg/kg administered as an intravenous infusion over 1 hour every 2 weeks) (Aflibercept draft SPC, 2013).

Generalisability of aflibercept trial results to the UK mCRC population

The eligibility criteria for VELOUR excluded the following groups: patients aged younger than 18 years; with prior irinotecan therapy; a history of major surgery within 28 days; severe acute or chronic medical condition that may have impaired the ability to participate in the study or interfered with the interpretation of results; a history of uncontrolled hypertension within 3 months before enrolment; deep vein thrombosis within 4 weeks before randomisation; and pregnant and breast-feeding women. It is expected that similar patient groups are likely to be excluded from treatment with aflibercept plus FOLFIRI in clinical practice.

Table B16 compares the characteristics of patients with mCRC included in the VELOUR study with those included in two observational studies conducted in the UK investigating resource use (the UK mCRC resource use study) and quality of life (the mCRC utilities study [M 11937], which also included patients in the Netherlands). Baseline characteristics of the patients in the UK-based studies were similar to the baseline characteristics of VELOUR patients, supportive of the generalisability of VELOUR to the UK population.

Table B16. **Comparison of characteristics of patients with mCRC in the VELOUR study and two real-life observational studies**

Baseline characteristic	Study EFC10262 (VELOUR)		[redacted]	[redacted]
	Aflibercept 4 mg/kg + FOLFIRI (n = 612)	Placebo + FOLFIRI (n = 614)		
ECOG PS, n (%)				
0	349 (57.0)	350 (57.0)	[redacted]	[redacted]
1	250 (40.8)	250 (40.7)	[redacted]	[redacted]
2	13 (2.1)	14 (2.3)	[redacted]	[redacted]
Prior bevacizumab,[a] n (%)				
Yes	186 (30.4)	187 (30.5)	[redacted]	[redacted]
No	426 (69.6)	427 (69.5)	[redacted]	[redacted]
Sex, n (%)				
Male	365 (59.6)	353 (57.5)	[redacted]	[redacted]
Female	247 (40.4)	261 (42.5)	[redacted]	[redacted]
Age, years				
Median (range)	61.0 (21-82)	61.0 (19-86)	[redacted]	[redacted]
Age > 65 years, %	33.5	38.9	[redacted]	[redacted]

Baseline characteristic	Study EFC10262 (VELOUR)		[redacted]	[redacted]
	Aflibercept 4 mg/kg + FOLFIRI (n = 612)	Placebo + FOLFIRI (n = 614)		
Number of metastatic organs involved at baseline (excluding primary site), n (%)				
0	2 (0.3)	6 (1.0)	[redacted]	[redacted]
1	256 (41.8)	271 (44.1)	[redacted]	[redacted]
> 1	354 (57.8)	337 (54.9)	[redacted]	[redacted]
Metastatic organs involved at baseline (excluding primary site), n (%)				
Any site	610 (99.7)	608 (99.0)	[redacted]	[redacted]
Liver	459 (75.0)	431 (70.2)	[redacted]	[redacted]
Lung	271 (44.3)	277 (45.1)	[redacted]	[redacted]
Lymph nodes	173 (28.3)	181 (29.5)	[redacted]	[redacted]
Peritoneum	68 (11.1)	88 (14.3)	[redacted]	[redacted]
Liver metastasis, n (%)				
No liver metastases, or liver and other metastases	459 (75.0)	468 (76.2)	[redacted]	[redacted]
Liver metastases only	153 (25.0)	146 (23.8)	[redacted]	[redacted]

ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, fluorouracil/leucovorin/irinotecan; mCRC, metastatic colorectal cancer; VELOUR, Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Colorectal Cancer After Failure of an Oxaliplatin Based Regimen.

[a] Prior bevacizumab status as provided at randomisation (stratification variable).

[b] Patients aged 65 years and older.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in appendix 10.

A systematic review was performed to identify cost-effectiveness studies relevant to this appraisal (economic analyses of aflibercept for the treatment of mCRC). This review was performed as part of a wider systematic review which also aimed to identify utility, resource use and cost estimates relevant to the appraisal. Full details of the systematic review are included in appendix 10.

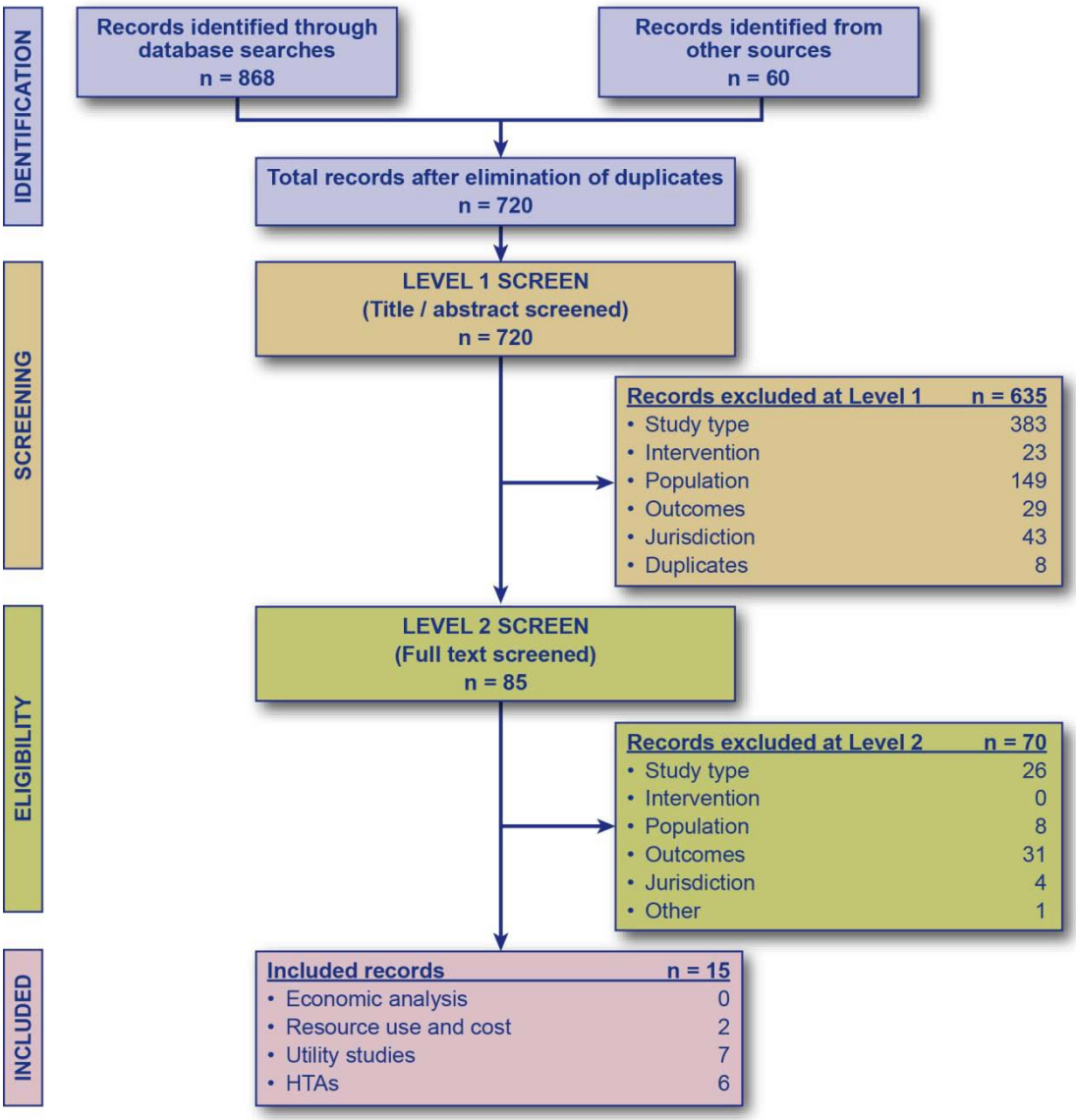
Searches were performed of MEDLINE, Embase, EconLit and the Cochrane Library (including NHS EED and the HTA databases). The database searches were limited to retrieval of publications after 1 January 2010 (published economic analyses for aflibercept were not expected before this date) and to English-language articles. The search terms were constructed to include MeSH and free-text terms for aflibercept and cost-effectiveness studies, as well as utility, resource use and cost studies.

Additional searches were performed for relevant conference abstracts (the two most recent meetings for selected clinical and economic conferences) and HTA agency Web sites (appraisals over the past 5 years). Reference lists of included economic analyses, reviews, and HTAs were reviewed for relevant studies.

A set of inclusion and exclusion criteria were applied to the search results, after duplicates were removed.

Figure B-9 presents the results in a PRISMA flow chart. The database searches yielded 868 citations; review of conference abstracts and searches of bibliographic reference lists yielded 60 citations. After elimination of duplicates, 720 studies were reviewed at Level 1 (based on titles and abstracts). Of these, 635 were excluded leaving 85 studies whose full text was reviewed at Level 2. No economic analyses of aflibercept for the treatment of mCRC were identified. Six HTAs were identified, none of aflibercept (these were included in the review to identify any relevant utility, resource use and cost estimates).

Figure B-9. **PRISMA diagram for the systematic review of economic and utility studies**



HTA, health technology assessment; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Description of identified studies

7.1.2 *Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.*

No studies were identified that assessed the cost-effectiveness of aflibercept.

7.1.3 *Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and*

Jefferson (1996)[1] or Philips et al., (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see appendix 11.

No studies were identified.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The patient population in the economic evaluation is patients with mCRC who are eligible for second-line combination chemotherapy and were previously treated with an oxaliplatin-based regimen. This is consistent with the licensed indication for aflibercept and the population of the VELOUR trial described in section 6.

Subgroup analyses also were performed for the following two patient groups:

- Patients with liver metastases only
- ITT population excluding patients who had received oxaliplatin as adjuvant-tbased therapy and relapsed within 6 months of this

Model structure

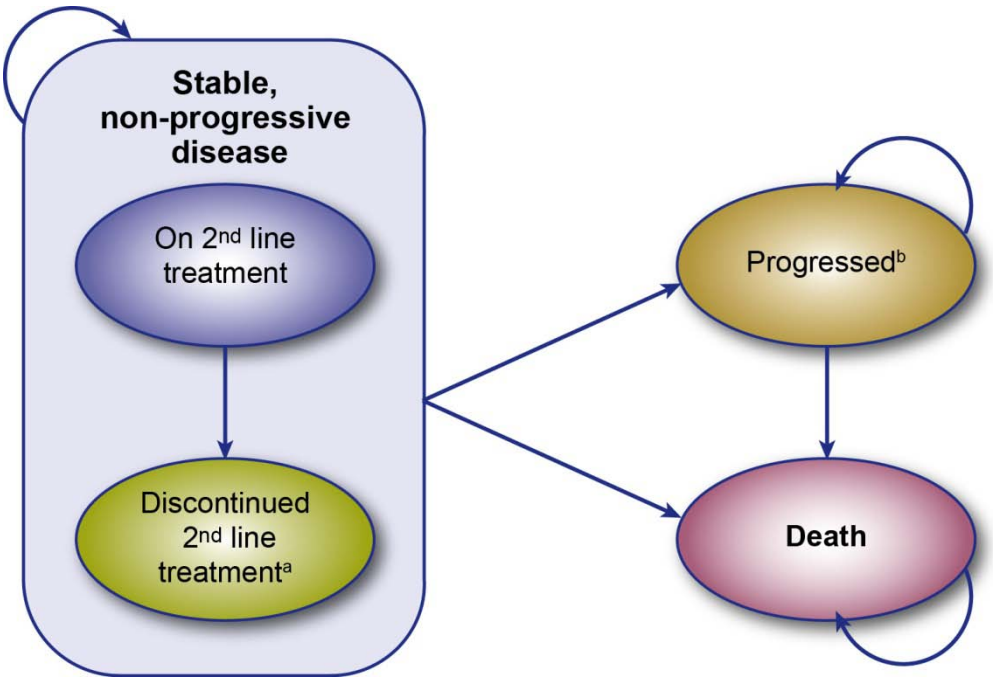
7.2.2 Please provide a diagrammatical representation of the model you have chosen.

Figure B-10 presents the model health states and transitions.

[1] Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996;313(7052):275-83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment, by Z Philips, L Ginnelly, M Sculpher, et al. Health Technol Assess. 2004;8:36.

Figure B-10. **Model structure**



[a] Patients who stopped second-line treatment due to adverse events or physician or patient preference.

[b] At least a 20% increase in the sum of the longest diameter of target lesions or unequivocal increase in the size of non-target lesions or the appearance of 1 or more new lesions. Includes both third-line and best supportive care patients who can be differentiated by costs and utilities.

All patients started in the "Stable, non-progressive disease" health state and the "On second-line treatment" substate. They could either stay in that substate or discontinue second-line treatment while remaining stable ("Stable, non-progressive disease - discontinued second-line treatment). They could also progress ("Progressed") or die ("Death").

Patients in the "Discontinued second-line treatment" state could either receive a further line of active therapy or best supportive care (BSC).

When a patient progressed, they either remained in the "Progression" health state or died. Upon disease progression, patients could receive further lines of active treatment and/or BSC.

As in routine clinical practice, in the VELOUR trial, patients could receive further lines of treatment after early discontinuation or progression; therefore, any potential effects on PFS or OS will already be captured in the outcomes observed. The probability of receiving subsequent therapy and the type of subsequent therapy was assumed to be the same in each treatment cohort, as observed within the VELOUR trial.

Patients were not allowed to move backwards in the model (i.e., they could not move contrary to the direction of the arrows in Figure B-10).

Adverse events were treated as events rather than health states in the model, with both the management costs and their effect on HRQL taken into account.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

Model structures which stratify patient-time into periods of stable progression-free disease, disease progression, and death are common in the economic evaluation of oncology treatments, and this structure is consistent with those used in previous health technology assessment of therapies for mCRC. The health states align with one of the key treatment goals, which is to prevent or delay disease progression for as long as possible. The health states also are aligned with the primary and secondary endpoints of the VELOUR trial: OS and PFS respectively. A fourth health state was added which split the Stable health state into "on treatment" and "post-treatment" phases. This approach was taken so that differences in costs and utilities experienced during treatment and after treatment whilst in PFS could be explored.

7.2.4 Please define what the health states in the model are meant to capture.

The model health states are defined inTable B17.

Table B17. **Definition of model health states**

Health state	Definition
Stable non-progressive disease, on second-line treatment	Patients who are receiving second-line treatment and whose disease has not progressed[a]
Stable non-progressive disease, discontinued second-line treatment	Patients who have discontinued second-line treatment (e.g., due to an adverse event, patient request, or investigator decision) and whose disease has not progressed[a] Patients may receive further active therapy and/or BSC
Progressed	Patients whose disease has progressed[a] Patients may receive further active therapy and/or BSC
Death	Patients who have died

BSC, best supportive care; IRC, independent review committee; PFS, progression-free survival.

[a] Disease progression was defined according to the criteria described in the VELOUR trial as follows:

- At least a 20% increase in the sum of the longest diameter of target lesions
- Unequivocal increase in the size of non-target lesions
- The appearance of one or more new lesions

On the basis of external expert opinion from the 2 advisory boards, progression based on IRC tumour assessment was used for the primary PFS analysis in the VELOUR trial and was selected as the base case for the model. A sensitivity analysis was conducted using PFS according to investigator assessment of progression.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The main aspects of the condition for patients and clinicians are disease progression (increase in lesion size or the appearance of new lesions) and death. Treatments received and the adverse events associated with these also are important. The model captures the impact of disease progression on HRQL by use of a specific health state. The costs and HRQL impact of treatment and adverse events are captured by use of an "on second-line treatment" health state.

In the model, the underlying disease progression was implemented for patients receiving aflibercept + FOLFIRI and those receiving FOLFIRI using parametric survival functions for PFS and OS fitted to data for each treatment group from the VELOUR trial. Details of this analysis are presented in section 7.3.1. The Kaplan-Meier curves for PFS and OS for each treatment group are presented in section 6.5.3.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Key features of the analysis are presented in Table B18.

Table B18. **Key features of analysis**

Factor	Chosen values	Justification	Reference
Time horizon	15 years	The model is designed to capture the lifetime costs and outcomes associated with aflibercept treatment. The log-logistic function has a decreasing hazard rate at the tail of the curve; to avoid generating unrealistically long survival times due to this decreasing rate, the survival curves were truncated at 15 years, which was considered realistic given the age and disease status of these patients.	See section 7.3.1
Cycle length	2 weeks	To reflect the biweekly treatment schedules.	Van Cutsem et al., 2010; VELOUR trial
Half-cycle correction	Yes	For completeness	None
Were health effects measured in QALYs; if not, what was used?	Yes	NICE Reference Case	NICE Methods Guide (NICE, 2008)
Discount of 3.5% for utilities and costs	Yes	NICE Reference Case	NICE Methods Guide (NICE, 2008)
Perspective (NHS/PSS)	Yes	NICE Reference Case	NICE Methods Guide (NICE, 2008)
FOLFIRI, fluorouracil/leucovorin/irinotecan; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; PSS, Personal Social Services; QALY, quality-adjusted life-year.			

Technology

7.2.7 *Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?*

Aflibercept + FOLFIRI and FOLFIRI were implemented in the model at the doses stated in Table B19. The dose for aflibercept is consistent with the marketing authorisation in this indication.

The regimens are summarised in Table B19.

Table B19. **Treatment regimens**

Regimen	**Details**	
FOLFIRI Given every 2 weeks	Irinotecan Day 1	180 mg/m^2 IV infusion over 90 minutes
	Leucovorin Day 1	400 mg/m^2 IV infusion over 2 hours at the same time in bags using a Y-line
	5-fluorouracil Day 1	400 mg/m^2 IV bolus given over 2-4 minutes, followed by 2,400 mg/m^2 continuous IV infusion over 46 hours
Aflibercept + FOLFIRI Given every 2 weeks	Aflibercept Day 1	4 mg/kg IV infusion over 1 hour given before the FOLFIRI regimen
	FOLFIRI Day 1	As above
FOLFIRI, fluorouracil/leucovorin/irinotecan; IV, intravenous.		

7.2.8 *Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators.*

Treatment is continued until disease progression or unacceptable toxicity occurs. Discontinuation may occur at the physician's discretion or due to patient preference. The duration of treatment with aflibercept + FOLFIRI and FOLFIRI in the model was based on the mean duration observed in the VELOUR trial [redacted] of patients in the aflibercept + FOLFIRI arm had not discontinued treatment within the study follow-up period[3]). Details of the estimation of second-line drug costs are presented in section 7.5.5.

It should be noted that the duration of treatment is greater than the average number of 2-week cycles of aflibercept or of FOLFIRI received due to dose delays or removal of one or both components of the cycle.

7.3 *Clinical parameters and variables*

7.3.1 *Please demonstrate how the clinical data were implemented into the model.*

Efficacy and safety inputs were derived from the patient level data of the VELOUR trial. The inputs for both the overall patient population and the subgroups were as follows:

- OS
- PFS
- Treatment discontinuation (2nd-line treatment discontinuation and early 2nd-line treatment discontinuation while in the stable health state)
- Adverse events (incidence and duration)

Parametric survival analysis was used to describe PFS, OS, time-to-treatment discontinuation, and time-to-early treatment discontinuation. The statistical analyses and selection of functions for the model were performed in accordance with the NICE Decision Support Unit recommendations (Latimer, 2011).

Separate analyses were performed for the ITT population and for each subgroup (i.e., subgroup analyses were performed using datasets specific to each subgroup rather than by using the using ITT dataset and including covariates). Functions were selected for the base-case analysis using diagnostic plots (e.g., log cumulative hazard plots), Akaike information criterion (AIC) and Bayesian information criterion (BIC) tests, visual inspection of fit to the Kaplan-Meier data, and consideration of the biological and clinical plausibility of the extrapolation beyond the end of trial follow-up.

[redacted]

Overall Survival

The parametric survival analysis for the OS endpoint is presented in section 6.5.3. The log-logistic functions fitted to each treatment group separately appeared to provide the best overall fit for OS for the two treatment groups and were selected for the base-case analysis; the Weibull and log-normal functions were explored in sensitivity analysis. Similar findings were observed for the subgroups (presented in section 7.9, and in appendix 14).

Progression-free Survival

For the base-case analysis, disease progression was as determined by IRC. Analyses in which progression was determined by investigator assessment were investigated in the sensitivity analysis.

In the VELOUR trial, the PFS curves showed an early separation and then converged after about 50 weeks (Figure B-11). All patients had progressed by the end of trial follow-up therefore no extrapolation was performed. Clear steps were observed in the Kaplan-Meier curves which are likely to be due to clustering of events around the scheduled screening visits. The fitting of parametric survival functions has a smoothing effect and results in the removal of these steps.

The AIC and BIC test results for the ITT population (IRC) are presented in Table B20; visual inspection plots are presented in Figure B-11 and Figure B-12. The log-cumulative hazard plots and further details of the analysis are presented in appendix 14.

Table B20. **AIC and BIC test results for PFS functions, ITT population**

Function	Aflibercept + FOLFIRI		Placebo + FOLFIRI		Both arms (proportional hazards)	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in red font indicate the lowest AIC and BIC values.

AIC, Akaike information criterion; BIC, Bayesian information criterion; FOLFIRI, fluorouracil/leucovorin/irinotecan; IRC, independent review committee; ITT, intention-to-treat; PFS, progression-free survival.

Note: PFS was as determined by IRC.

Figure B-11. **PFS functions and Kaplan-Meier data for the aflibercept + FOLFIRI arm, ITT population: functions fitted to each treatment arm separately for (A) aflibercept arm and (B) placebo arm**

[redacted]

FOLFIRI, fluorouracil/leucovorin/irinotecan; ITT, intention-to-treat; PFS, progression-free survival. (12cycles = 6 months; 24 cycles = 52 weeks)

Figure B-12. **PFS functions and Kaplan-Meier data for the placebo + FOLFIRI arm, ITT population: functions fitted to both treatment arms with treatment as predictor (assuming proportional hazards) for (A) aflibercept arm and (B) placebo arm**

[redacted]

FOLFIRI, fluorouracil/leucovorin/irinotecan; ITT, intention-to-treat; PFS, progression-free survival.

[redacted] (appendix 14). Functions fitted separately to data for each treatment group are described below.

- For the aflibercept + FOLFIRI arm, the lowest AIC and BIC results were obtained for the Weibull function, followed by the log-logistic and log-normal functions (which had similar results) and the exponential function. On visual inspection, the Weibull function followed the Kaplan-Meier data most closely and predicted that all patients reached the PFS endpoint at a similar time to that observed in the trial (i.e., the times at which the functions and the Kaplan-Meier curves hit the x-axis were similar). The log-logistic and log-normal functions did not provide a plausible fit on visual inspection; both functions substantially overestimated PFS between weeks 40 and 120 (cycles 20 and 60).
- For the placebo + FOLFIRI arm, the lowest AIC and BIC results were obtained for the log-normal function, followed by the log-logistic, Weibull and exponential functions. On visual inspection, the log-normal function appeared to follow the Kaplan-Meier data most closely, but it overestimated PFS after 60 weeks (30 cycles) and predicted that all patients reached the PFS endpoint later than observed in the trial. The log-logistic function overestimated PFS after 60 weeks (30 cycles). The Weibull function underestimated PFS slightly after 40 weeks (20 cycles) and predicted that all patients reached the PFS endpoint earlier than observed in the trial.

In the absence of a strong justification, it is not appropriate to apply different functions to two treatment groups for the same endpoint (Latimer, 2011). The Weibull functions appeared to provide the best overall fit for PFS in both treatment groups and were selected for the base-case analysis; the log-logistic functions, log-normal functions and Kaplan-Meier data were explored in sensitivity analysis.

[redacted]

The findings for the subgroups are presented in section 7.9.

Time to Treatment Discontinuation

Parametric survival functions for “time to second-line treatment discontinuation” and “time to early second-line treatment discontinuation” (prior to disease progression) were used to govern the time spent in the two stable, non-progressive disease health states (“On second-line treatment” and “Discontinued second-line treatment”). These substates were distinguished so that the impact of treatment on HRQL and the cost of further lines of therapy and BSC could be explored. The costs of second-line treatment were not based on the time spent in the “On second-line treatment” substate; they were calculated separately based on the mean duration of treatment, mean number of administrations and mean dose actually received in the VELOUR trial (see section 7.5.5), so that they could accurately reflect dose reductions and dose delays as observed in the trial.

The survival functions were fitted in the same way as for the PFS and OS endpoints (described above). Details are provided in appendix 14. The AIC and BIC test results are presented in Table B21 and Table B22 and visual inspection plots are presented in Figure B-13 and Figure B-14. Weibull functions fitted separately to data for each treatment group were selected for the base-case analysis.

Table B21. **AIC and BIC test results for time to second-line treatment discontinuation functions, ITT population**

Function	Aflibercept + FOLFIRI		Placebo + FOLFIRI		Both arms (proportional hazards)	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in red font indicate the lowest AIC and BIC values.

AIC, Akaike information criterion; BIC, Bayesian information criterion; FOLFIRI, fluorouracil/leucovorin/irinotecan; ITT, intention-to-treat.

Table B22. **AIC and BIC test results for time to early second-line treatment discontinuation functions, ITT population**

Function	Aflibercept + FOLFIRI		Placebo + FOLFIRI		Both arms (proportional hazards)	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in red font indicate the lowest AIC and BIC values.

AIC, Akaike information criterion; BIC, Bayesian information criterion; FOLFIRI, fluorouracil/leucovorin/irinotecan; ITT, intention-to-treat.

Figure B-13. **Time to second-line treatment discontinuation functions and Kaplan-Meier data, ITT population**

[redacted]

Figure B-14. **Time to early second-line treatment discontinuation functions and Kaplan-Meier data, ITT population**

[redacted]

Adverse Events

Grade 3 and 4 treatment-emergent adverse events that affected more than 5% of the population in the VELOUR trial were included in the evaluation, together with six additional rarer adverse events that were considered relevant by the clinical advisory board (Table B23).

The model applied the event rate per patient-time on treatment. Table B23 presents the number of events observed in each treatment arm and the total patient-time on treatment (expressed as the number of 2-week model cycles) for the ITT population. The aggregate rate of adverse events (per 2-week model cycle) was calculated as the total number of events divided by total number of 2-week periods on treatment.

Table B23. **Adverse events**

	Aflibercept + FOLFIRI	**FOLFIRI**
Total number of patients	[redacted]	[redacted]
Total patient-time on treatment (number of 2-week model cycles)	[redacted]	[redacted]
Adverse event	**Number of events**	
Diarrhoea	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]
Infections	[redacted]	[redacted]
Hand-foot syndrome	[redacted]	[redacted]
Gastrointestinal perforation	[redacted]	[redacted]
Haemorrhage	[redacted]	[redacted]
Febrile neutropaenia	[redacted]	[redacted]
Neutropaenia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Total	[redacted]	[redacted]
Event rate per model cycle	[redacted]	[redacted]

Source: VELOUR trial.

Note that the data presented in the table differ from that presented in section 6.9.2, because these data represent the number of events rather than the number of patients with events (patients may experience more than one adverse event). The model applies the number of events rather than patients with events to account for the impact of multiple events in individual patients.

In the subgroup analysis, data specific to each subgroup were applied (presented in Appendix 15)

7.3.2 *Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.*

Time-dependent transition probabilities for early second-line treatment discontinuation, second-line treatment discontinuation and death were calculated from the parametric survival functions using the general formula:

$$p_t = [S(t) - S(t - u)] / S(t),$$

where:

- p_t is the transition probability at time t
- S(t) is the survival at time t
- u is the model cycle length (2 weeks)

The number of patients in the "Progressed" health state was calculated as the total number entering the model minus the number in the "Stable, non-progressive disease" and the "Dead" health states.

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

Evidence that transition probabilities vary over time exists in the finding that the exponential function did not provide the best fit to the PFS, OS and time to treatment discontinuation data. The model utilised time-dependent transition probabilities as described in sections 7.3.1 and 7.3.2.

7.3.4 *Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?*

Life-years were estimated directly from OS data without linkage via intermediate outcomes. QALYs were estimated by linking utility weights to the health states "Stable, non-progressive disease" ("On second-line treatment" and "Discontinued second-line treatment"), "Progressed," and "Death" and applying disutilities due to adverse events. Time spent in the health states was estimated directly from survival functions fitted to data from the VELOUR trial for time to second-line treatment discontinuation, PFS, and OS.

7.3.5 *If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:*

- *The criteria for selecting the experts*
- *The number of experts approached*
- *The number of experts who participated*
- *Declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought*
- *The background information provided and its consistency with the totality of the evidence provided in the submission*
- *The method used to collect the opinions*
- *The medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)*
- *The questions asked*
- *Whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).*

No clinical parameters were estimated by clinical experts. A clinical and economic advisory board reviewed the model parameters alongside the model structure and advised on their appropriateness. Three advisory board meetings were held, one during the model design phase and two after completion of the model.

Summary of selected values

7.3.6 *Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.*

A summary of the variables included in the cost-effectiveness analysis is presented in Table B24. Parameters which were adjusted in the subgroup analyses (using data specific to the subgroup) are indicated (superscripted a).

Table B24. **Summary of variables applied in the economic model**

Variable	Value	Distribution	Reference to section in submission
Mean weight (kg)[a]	75.31	SE = 0.24 (gamma)	VELOUR, WE (estimated from

[4] Adapted from Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee; 2008.

Variable	Value	Distribution	Reference to section in submission
			patient-level data)
BSA (m^2)[a]	1.85	SE = 0.003 (gamma)	VELOUR, WE (estimated from patient-level data)
PFS, OS, time to second-line treatment discontinuation[a]	Survival function parameters	SE and VCVM (correlated normal, Cholesky decomposition)	VELOUR, sections 7.3.1, (appendix 14)
AE probabilities[a]	Number of events per cycle	Number of events and total number of patients (beta)	VELOUR, section 7.3.1
Utility weights			
Stable, on second-line therapy	[redacted]	[redacted]	[redacted]
Stable, discontinued second-line therapy	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]
Dead	0	Fixed	Assumption
Disutilities for AEs	Various	SE assumed to be [redacted] of mean (beta for the decrement)	Section 7.4.9
Mean duration of second-line treatment (2-week model cycles)			
Aflibercept + FOLFIRI[a,c]	[redacted]	SE = 0.35 (gamma)	VELOUR, section 7.5.5
FOLFIRI[a,c]	[redacted]	SE = 0.365 (gamma)	VELOUR, section 7.5.5
Mean cost of subsequent chemotherapy and supportive drugs			
Pre-progression, active Tx (total per patient receiving active Tx)[d]	[redacted]	SE for percentage of patients for each Tx = 30% of mean value (Dirichlet)	Sanofi retrospective observational study (UK mCRC resource use study), sections 7.5.3
Post-progression, active Tx (total per patient receiving active Tx)[d]	[redacted]		
BSC (supportive drugs,	[redacted]	SE for	

Variable	Value	Distribution	Reference to section in submission
pre- or post-progression; per cycle)[e]		cost = 30% of mean value (gamma)	and (appendix 15) SE is an assumption
Mean cost of patient management in each health state			
Stable, on second-line therapy	[redacted]	SE for cost = 30% of mean value (gamma)	Sanofi retrospective observational study (UK mCRC resource use study) and Physician Survey, sections 7.5.3, 7.5.4 and appendix 15) SE is an assumption
Stable, discontinued second-line therapy			
Regimen change (total)	[redacted]		
Management of patients on active Tx (lump sum)	[redacted]		
Management of patients on BSC (per cycle)	[redacted]		
Progressed			
Regimen change (total)	[redacted]		
Management of patients on active Tx (per cycle)	[redacted]		
Management of patients on BSC (per cycle)	[redacted]		

AE, adverse event; BSA, body surface area; BSC, best supportive care; FOLFIRI, fluorouracil/leucovorin/irinotecan; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; SE, standard error; Tx, treatment; VCVM, variance-covariance matrix; WE, Western European population of the VELOUR trial.

[a] Indicates parameters that were adjusted in the subgroup analyses (using data specific to the subgroup).

[b] Calculations include dose adjustment for patient weight and BSA, dose reductions and delays (e.g., for toxicity) and drug wastage.

[c] The mean duration of treatment includes dose delays (and therefore does not equal mean chemotherapy cycles × 2 weeks).

[d] Average one-off cost applied for patients who receive active treatment).

[e] Average costs per cycle applied for patients receiving BSC only [redacted]

[f] Active Tx for patients in the "Stable, discontinued second-line" and "Progressed" health states was assumed to continue for a finite number of cycles [redacted] and did not continue until death in all patients..

7.3.7 *Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.*

All patients experienced disease progression during the VELOUR trial; therefore, there was no need for extrapolation of PFS (although, as described above, parametric functions were fitted to smooth the curves).

Survival was extrapolated beyond the end of trial follow-up using parametric survival functions fitted individually to the OS data for the aflibercept + FOLFIRI and the placebo + FOLFIRI arms of the VELOUR trial. The assumption was made that the survival functions fitted to the empirical trial data for each treatment group may be extrapolated beyond the trial follow-up period. The majority of patients died within the trial follow-up (OS was approximately [redacted] for placebo + FOLFIRI and [redacted] for aflibercept + FOLFIRI at end of follow-up); therefore, the uncertainty associated with the extrapolation is less than in many oncology models where a greater degree of extrapolation is required.

Details of the survival analysis, the justification for the functions that were selected for the model, visual inspection plots presenting the survival functions alongside the Kaplan-Meier curves, and a discussion of the biological and clinical plausibility of the extrapolation are presented in section 6.5.3 and 7.3.1.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Assumptions made in the model and their justifications are presented in Table B25.

Table B25. **Assumptions made in the economic model**

Assumption	Discussion and justification
The efficacy and safety data from the VELOUR trial is applicable to the eligible patient population in the UK, and the outcome differences observed in the trial translate to the patient population in routine clinical practice in the UK	VELOUR was a multicentre trial [redacted] were treated in the UK. Table B16 in Section 6.10.4 shows similar patient characteristics in the VELOUR trial to two observational studies completed within the UK.
OS observed during the VELOUR follow-up period can be extrapolated to the modelled time horizon	See sections 6.5.3, 7.3.1 and 7.3.7
Resource use based on the UK observational study (UK mCRC resource use study) and physician survey is representative of clinical practice in the UK	The resource use data for secondary care came from an observational study (UK mCRC resource use study) in four UK centres and are expected to be representative of the UK practice as a whole.
Medication usage observed in the western European population of the VELOUR trial is representative of that in routine clinical practice in the UK	The weight and BSA distribution of the western European population of the VELOUR trial is expected to more accurately represent that of the UK population than the entire VELOUR population (which included patients from, Asia Pacific, Eastern Europe, Russia, South America, South Africa, and the United States)
Disease management costs and	There is no reason or evidence to suggest the cost

Assumption	Discussion and justification
subsequent treatments are assumed to be the same for all subgroups of interest as for the overall patient population	of disease management would be significantly different between different subgroups.
There is no difference in the cost of end-of-life care between cohorts of patients receiving alternative interventions (the cost of end-of-life care is omitted from the model)	Every patient receives end-of-life care for a short period prior to death; therefore, no incremental difference in costs is expected according to the second-line therapy received.
The cost of managing AEs does not depend on the health state that the patient is in or the type of treatment administered	This is a common assumption of economic analyses; data specific to each health state are not available
The rate of AEs is constant over the treatment period	In practice, AEs are more likely to be experienced early in the treatment period (true in VELOUR for grade 3-4 AEs). This assumption may underestimate the cost of AEs for each cohort (since costs are discounted), which would favour aflibercept + FOLFIRI because the cost of AEs is greater in this group. However, because there is little treatment after the first year, this effect is likely to be negligible
The duration of AEs is assumed to be the same for all subgroups as for the overall patient population	There is no reason or evidence to suggest the duration of AEs would vary between subgroups.
Utility values are assumed to depend only on the health state a given patient is in and not on the treatment arm (except for the "Stable, no progressive disease, on second-line treatment" health state, where intervention-specific utilities are applied)	This is a common assumption of economic analyses; data specific to each intervention are not available
The utility weights estimated in the mCRC utilities study are applicable for the population eligible for aflibercept + FOLFIRI in routine clinical practice in England and Wales	The mCRC utilities study was conducted in two sites in the UK (50 patients) and two sites in the Netherlands (21 patients) using the EQ-5D (TTO tariffs; Dolan, 1997). Simple selection criteria were designed to recruit a study population consistent with the population that would be eligible to receive aflibercept + FOLFIRI in routine clinical practice (i.e., within the licensed indication) or were in subsequent phases of disease progression. The health states in the study were defined in the same way as the model health states. See section 7.4.6, 7.4.9 and (appendix 15)
The disutilities for AEs are assumed not to differ between different types of cancers	This is a common assumption of economic analyses; data specific to patients with mCRC are not available
Utility values have been assumed to be the same for all subgroups of interest as for the overall population	There is no reason or evidence to suggest utility would vary between subgroups
AE, adverse event; BSA, body surface area; FOLFIRI, fluorouracil/leucovorin/irinotecan; mCRC,	

Assumption	Discussion and justification
metastatic colorectal cancer; OS, overall survival; UK, United Kingdom.	

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Many people with mCRC do not have any symptoms. If symptoms do occur, the most common are as follows:

- A change in bowel habits, such as frequent diarrhoea or constipation
- Loss of appetite and nausea
- Abdominal pain
- Unexplained weight loss
- Fatigue

Other symptoms may occur, depending on the site(s) of metastasis:

- Peritoneal disease causes ascites, which may cause bloating, a swollen abdomen, loss of appetite, or a feeling of fullness.
- Liver metastases may cause loss of energy, loss of appetite, weight loss, nausea, and right upper quadrant discomfort.
- Lung metastases may cause coughing, coughing up blood (haemoptysis), or breathing difficulties.
- Bone metastases may cause bone pain, especially in the back, hips, and pelvis.
- Brain metastases may cause headache, seizures, altered vision, impaired mobility, and nausea.

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

For patients with stable, nonprogressive disease, HRQL may be expected to be reasonably stable as their disease is being actively controlled with chemotherapy. For patients with disease progression, symptoms associated with their metastases may worsen, leading to deterioration in HRQL over time. HRQL changes in the progressive disease state are likely to depend on subsequent management – those progressing after second-line therapy may receive further-line active therapy which controls their disease for a further period of time, or may receive best supportive care which provides symptomatic control, helping to stabilise HRQL. However, it is expected that all patients will inevitably experience substantial deterioration in quality of life during the very end stage of the disease.

HRQL data derived from clinical trials

7.4.3 *If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.*

- *Method of elicitation.*
- *Method of valuation.*
- *Point when measurements were made.*
- *Consistency with reference case.*
- *Appropriateness for cost-effectiveness analysis.*
- *Results with confidence intervals.*

Health-related quality of life data for patients receiving aflibercept + FOLFIRI are being collected in the ASQoP study (AFLIBC06097) using the EQ-5D (version 4), EORTC QLQ-C30 (version 3) and EORTC QLQ-CR29. Details of this study are provided in section 6.8.1. Briefly, measurements are being made in approximately 900 patients (50 in the UK) at baseline at the beginning of every odd chemotherapy cycle (day 1 of cycle 3, 5, etc; prior to drug administration) and at the end of treatment visit. Utility weights will be estimated from the EQ-5D descriptive system data by application of the UK time trade-off tariffs (Dolan, 1997).

However, the data from this study are not yet mature and therefore not appropriate for use in the cost-effectiveness analysis at this point in time. [redacted] Further data are expected to become available during the course of this technology appraisal process.

Mapping

7.4.4 *If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.*

- *Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.*
- *Details of the methodology used.*

Details of validation of the mapping technique.

No mapping was performed to transform utilities or quality of life data in clinical trials.

HRQL studies

7.4.5 *Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 12.*

A systematic review was performed to identify utility estimates relevant to this appraisal. This review was performed as part of a wider systematic review described previously (section 7.1) which also aimed to identify cost-effectiveness studies of aflibercept, resource use estimates and cost estimates relevant to the appraisal. Full details of the systematic review are included in appendix 10.

The searches, inclusion criteria and exclusion criteria were designed to identify the following:

- Utility studies for mCRC
- Utility studies for adverse events related to second-line treatments in patients with mCRC (diarrhoea, hypertension, fatigue, stomatitis, abdominal pain, vomiting, dehydration, decreased appetite, nausea, neuropathy, infections, hand-foot syndrome, gastrointestinal perforation, haemorrhage, and febrile neutropaenia).

The following study types were excluded:

- Quality of life studies that did not report utility weights
- Utility studies that did not report primary data (i.e., estimates were referenced to other reports); in this event, the original reports of the referenced studies were screened for inclusion in the review and included where appropriate
- Utility studies where no relevant health states were investigated

Figure B-9 in section 7.1 presents the results in a PRISMA flow chart. Six utility studies and one study reporting SF-36 data were identified. In addition, utility estimates were reported in the documentation for five HTAs.

An observational study collecting utility data has been performed by Sanofi; this study is complete but is not yet published (mCRC utilities study).

7.4.6 Provide details of the studies in which HRQL is measured.

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Details of the studies identified are presented in Table B26. An assessment of the consistency of the estimates with the NICE Reference Case and their appropriateness for use in the cost-effectiveness analysis is presented in Table B27. The unpublished Sanofi observational utility study (mCRC utilities study) is summarised in the text following Table B27.

Table B26. **Utility-weight estimates identified by the systematic review**

First author (year)	Study population[a]	Methods of elicitation and valuation[b]	Description	Utility estimate[c]
Austin, 2010	37 patients who underwent pelvic exenteration for locally advanced primary or recurrent rectal cancer in Australia. An information pack was mailed to eligible patients and consenting patients were then contacted by telephone to complete the QoL assessment.	SF-36 version 2 and FACT-Colorectal administered by telephone. Only the 2 component scores for physical and mental health have been assessed because the 8 dimensions of the SF-36 version 2 are affected by age, gender, and country and because of the small case group. Norm-based scores were used to represent the data for patients who underwent pelvic exenteration and these were compared with the norm-based scores of the general Australian population.	**SF-36 Physical component score**	**Mean (SD)**
			Patients with pelvic exenteration (n = 37)	44.7 (9.5)
			Australian population (n = 3,014)	50.3 (9.7)
			SF-36 Mental component score	
			Patients with pelvic exenteration (n = 37)	53.5 (11.7)
			Australian population (n = 3014)	52.9 (10.2)
AWMSG, 2010	The CO17 trial contained 572 patients randomised to receive either cetuximab + BSC or BSC alone.	QoL assessed at multiple time points in study CO17, using a generic instrument. This has been used to derive utility values for pre- and post-progression health states. Utility values for patients receiving cetuximab monotherapy were assumed for patients receiving cetuximab + irinotecan.	No utility estimates reported	
Bennett, 2011	The first-line trial compared the efficacy and safety of panitumumab +	HRQL was measured using the EQ-5D Health State Index and the EQ-5D VAS. Assessments were taken at baseline and monthly until disease progression and	**First-line trial**	**Baseline (SD)**
			Panitumumab + FOLFOX4 (n = 284)	0.778 (0.247)
			FOLFOX4 (n = 292)	0.756 (0.244)

First author (year)	Study population[a]	Methods of elicitation and valuation[b]	Description		Utility estimate[c]
	FOLFOX4 with FOLFOX4 alone in 576 patients with previously untreated mCRC. The second-line trial compared the efficacy and safety of panitumumab + FOLFIRI with FOLFIRI alone in 530 patients with previously treated mCRC.	then once at the 4-week safety follow-up visit. Total score for EQ-5D generated using published UK tariffs (Dolan, 1997).	**Second-line trial**		
			Panitumumab + FOLFIRI (n = 263)		0.769 (0.230)
			FOLFIRI (n = 267)		0.762 (0.252)
Best, 2010	49 patients in the US with Stage II-IV colon cancer and 49 community members. Patients were approached by clinic staff at the USC Norris Cancer Center at the University of Southern California to assess their willingness to participate in the study. A convenience sample of community members also was recruited; an effort was made to recruit subjects who were similar to patients	The TTO technique was used to elicit preferences for 7 health states associated with colon cancer and its treatment. These health states were developed using a survey to identify problems and the intensity with which patients with colon cancer experienced such problems. Subjects completed the EQ-5D Health Status Questionnaire and VAS to categorise their current health. Preference assessment was done using a TTO preference elicitation board that consisted of a description for Perfect Health, Health State "B", and a time scale indicating the maximum period of life that may be traded. Note: Adjusted TTO values were based on regression analysis, including dummy	**Current health (EQ-5D single index score)**		**Mean (95% CI)**
			Patients with colon cancer		0.86 (0.82-0.90)
			Community members		0.92 (0.89-0.95)
			Transformed VASs		
			Health state	**Patients mean/n (95% CI)**	**Community mean/n (95% CI)**
			Remission	0.950/49 (0.932-0.969)	0.933/49 (0.916-0.951)
			Metastatic, stable	0.606/25 (0.499-0.712)	0.643/30 (0.555-0.732)
			Metastatic, progressive	0.527/27 (0.432-0.623)	0.304/27 (0.219-0.389)
			Current health	0.943/49 (0.920-0.967)	0.969/49 (0.950-0.987)

First author (year)	Study population[a]	Methods of elicitation and valuation[b]	Description			Utility estimate[c]	
	participating in this study with respect to demographic characteristics such as gender and age.	variables for 7 chronic health states and covariates age, education, and current health. Adjusted means were based on 60-year-old with mean education and mean TTO for current health.	**TTO scores**				
			Health state	**Patients**		**Community**	
				Raw	**Adjusted**	**Raw**	**Adjusted**
			Remission	0.87	0.83	0.83	0.82
			Metastatic, stable	0.46	0.40	0.54	0.51
			Metastatic, progressive	0.38	0.37	0.21	0.21
			Current health	0.82	—	0.94	—
Dranitsaris, 2011	Patients with mCRC receiving chemotherapy with and without bevacizumab. Utility values were derived from a convenience sample consisting of 24 oncology nurses. This patient surrogate group was used as a compromise to provide insight from both the perspective of the patient and the general public.	TTO technique used to derive healthy month equivalents, using a standardised questionnaire supported by printed interview tools and graphical displays. To minimise the framing effect, all pathways were presented pictorially in a consistent manner. Demographic data were collected from each participant, including years of oncology and colorectal cancer experience, involvement in the development of systemic treatment guidelines for colorectal cancer, familiarity with the cost of anti-cancer drugs, and family history of colorectal cancer.	**Health outcomes evaluated in the decision model**			Mean (95% CI)	
			FOLFOX + “new drug” was discontinued after 2 cycles due to side effects, and the patient then was treated with FOLFIRI for 4 cycles. There was disease progression. The patient received BSC and died 6 months later.			0.74 (0.65-0.83)	
			FOLFOX + “new drug” was discontinued after 2 cycles due to side effects, and the patient then was treated with FOLFIRI. There was a response to FOLFIRI, and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 22 months later.			0.80 (0.73-0.87)	

First author (year)	Study population[a]	Methods of elicitation and valuation[b]	Description	Utility estimate[c]
			FOLFOX + "new drug" was discontinued after 2 cycles due to side effects, and the patient then was treated with FOLFIRI. There was a response to FOLFIRI, and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 2 months later.	0.67 (0.61-0.73)
			FOLFOX + "new drug" was discontinued after 2 cycles due to side effects, and the patient was then treated with FOLFIRI for 2 cycles. However, the patient died due to cancer progression within the first 2 months.	0.74 (0.65-0.84)
Dranitsaris, 2012	Patients with mCRC receiving chemotherapy with and without bevacizumab. Utility values were derived from a convenience sample consisting of 24 oncology nurses and pharmacists in Spain.	Using the TTO technique, quality-adjusted life periods were measured as "healthy months equivalent" for the time spent in each outcome of the decision model. Each participant was interviewed for 15-30 minutes by a trained local investigator. Respondents were presented with information on FOLFOX, bevacizumab, and FOLFIRI consisting of the methods of administration, efficacy, and the side effects reported in the literature. The respondents then were asked how many months of "optimal health" they considered being equivalent to the time spent in each of the less than optimal	**Health outcomes evaluated in the decision model**	**Mean (95% CI)**
			Stopped FOLFOX + "new drug" after 2 cycles due to side effects, and the patient then was treated with FOLFIRI for 4 cycles. There was disease progression. The patient received BSC and died 6 months later.	0.53 (0.46-0.60)
			Stopped FOLFOX + "new drug" after 2 cycles due to side effects, and the patient then was treated with FOLFIRI. There was a response to FOLFIRI, and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 22 months later.	0.65 (0.57-0.87)

First author (year)	Study population[a]	Methods of elicitation and valuation[b]	Description	Utility estimate[c]
		health states described in the model. A standardised questionnaire supported by printed interview tools with graphical displays was used to facilitate the participant's understanding of the TTO technique. To minimise the framing effect, all pathways were presented in a consistent manner pictorially.	Stopped FOLFOX + "new drug" after 2 cycles due to side effects, and the patient then was treated with FOLFIRI. There was a response to FOLFIRI, and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 2 months later.	0.67 (0.58-0.76)
			Stopped FOLFOX + "new drug" after 2 cycles due to side effects, and the patient then was treated with FOLFIRI for 2 cycles. However, the patient died due to cancer progression within the first 2 months.	0.52 (0.42-0.62)
NICE, 2009	The CRYSTAL trial comparing cetuximab with FOLFIRI with FOLFIRI alone in patients with previously untreated mCRC with non-resectable metastases and an ECOG performance status ≤ 2 at study entry.	Utility estimates were generated using EQ-5D scores from patients enrolled in the CRYSTAL trial. Only 37 patients completed evaluable baseline EQ-5D questionnaires; therefore, no formal statistical analyses were performed. A summary of utility estimates was calculated for all patients, pooling all values at each visit.	First-line chemotherapy	0.77
NICE, 2010	The NO16966 study demonstrating the non-inferiority of XELOX compared with FOLFOX4 in adult patients with	First-line chemotherapy estimate taken from CRYSTAL trial and TA176. Post first-line without disease progression estimate based on expert opinion. Second-line PFS estimate was the same	First-line chemotherapy	0.77
			Post first-line chemotherapy without disease progression	0.79
			Second-line PFS	0.73
			With disease progression	0.68

First author (year)	Study population[a]	Methods of elicitation and valuation[b]	Description	Utility estimate[c]
	histologically confirmed mCRC who had not been previously treated with chemotherapy.	assumption made in the Merck submission for cetuximab (NICE, 2009) (equivalent to the average of the first- and third-line utility values). With disease progression estimates taken from a trial of cetuximab for the third-line treatment of mCRC and using the HUI questionnaire.		
NICE, 2011	Full clinical guidance for the diagnosis and management of colorectal cancer.	Utility estimates obtained from a published study of elicited preference values for health states associated with colon cancer (Best, 2010). The study used TTO techniques to elicit preferences from both patients and community members. Estimates obtained from a utility study conducted in metastatic breast cancer were used as a proxy to capture the impact of treatment-related toxicity on patient well-being (Lloyd, 2006).	**Health state**	**Value**
			Metastatic disease, stable	0.51
			Metastatic disease, progressive	0.21
			Disutility febrile neutropaenia	–0.15
			Disutility grade 3/4 diarrhoea	–0.103
			Disutility grade 3/4 hand-foot syndrome	–0.116
NICE, 2012	The CO17 trial, which compared cetuximab plus BSC with BSC alone in 572 patients with mCRC who had been previously treated with a fluoropyrimidine, irinotecan, and oxaliplatin or who had contraindications to	Merck Serono obtained estimates of utility for each health state using the HUI scale, a generic preference-based measure of QoL, by reanalysing data by health state in the CO17 trial. These utility values then were applied to cetuximab plus irinotecan and BSC and panitumumab plus BSC. The Assessment Group questioned the validity of the utility values obtained from	**Health state**	**Utility value**
			Manufacturer	
			Progression-free disease	0.809
			Progressive disease	0.789
			Assessment Group	
			Progression-free disease	
			Cetuximab plus BSC	0.81

First author (year)	Study population[a]	Methods of elicitation and valuation[b]	Description	Utility estimate[c]
	these treatments.	the CO17 trial by Merck Serono because the values exceeded those values produced by the health economic evaluation that accompanied the trial (Mittmann, 2009). The Assessment Group obtained estimates of utility for the Mittmann (2009) study that used individual patient-level data and HUI data from the CO17 trial.	BSC	0.75
			Cetuximab plus irinotecan	0.75
			Panitumumab plus BSC	0.87
			Progressive disease (all treatments)	0.69
Odom, 2011	463 patients with EGFR-detectable mCRC and documented evidence of disease progression after failure of fluoropyrimidines and pre-specified exposure to oxaliplatin and irinotecan were randomly assigned to receive panitumumab plus BSC every 2 weeks or BSC alone.	Overall HRQL was measured at baseline and monthly until disease progression, using the EQ-5D Index. The index score was calculated by combining scores from the 5 dimensions, using population-based preference weights (Shaw, 2005).	**Treatment group**	**Mean (SD) at baseline**
			Panitumumab plus BSC	
			Overall	0.72 (0.24)
			Wild-type *KRAS*	0.73 (0.24)
			Mutant *KRAS*	0.71 (0.25)
			BSC alone	
			Overall	0.68 (0.25)
			Wild-type *KRAS*	0.68 (0.23)
			Mutant *KRAS*	0.68 (0.26)
Wiering, 2011	145 patients with a history of proven	The EQ-5D was used as a generic value-based HRQL instrument. The EQ-5D	**Health state**	**Mean/no. observations (SD)**

First author (year)	Study population[a]	Methods of elicitation and valuation[b]	Description	Utility estimate[c]
			Disease-free	0.78/891 (0.23)
			Non-curative	0.67/162 (0.31)
			Recurrence	0.74/450 (0.25)
			Without chemotherapy	0.82/205 (0.17)
			With chemotherapy	0.68/245 (0.28)

AWMSG, All Wales Medicines Strategy Group; BSC, best supportive care; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EQ-5D, EuroQoL 5-dimension health questionnaire; FACT, Functional Assessment of Cancer Therapy; FOLFIRI, irinotecan plus 5-fluorouracil/leucovorin; FOLFOX, oxaliplatin plus 5-fluorouracil/leucovorin; FOLFOX4, leucovorin 200 mg/m^2 as a 2-hour infusion, followed by bolus 5-fluorouracil 400 mg/m^2 and a 22-hour infusion of 5-fluorouracil 600 mg/m^2 for 2 consecutive days every 14 days, plus a 2-hour infusion of 85 mg/m^2 of oxaliplatin on day 1, given simultaneously with leucovorin; HRQL, health-related quality of life; HUI, Health Utility Index; KRAS, Kirsten rat sarcoma viral oncogene homolog; mCRC, metastatic colorectal cancer; NICE, National Institute for Health and Clinical Excellence; PFS, progression-free survival; QoL, quality of life; SD, standard deviation; SF-36, Short-Form 36-Item Health Survey; TTO, time tradeoff; UK, United Kingdom; US, United States; VAS, visual analogue scale; XELOX, capecitabine and oxaliplatin.

[a] Includes information about recruitment, country, sample size, response rate, and interventions received (if any).

[b] Includes elicitation methods (including instrument used), valuation methods, and any mapping performed.

[c] Includes tabulation of 95% CIs or another measure of uncertainty.

Table B27. **Consistency of utility estimates with the NICE reference case**

First author, year	Measured in patients	Values reflect public preferences using choice-based method	EQ-5D/other method used	Utility scale 1 = full or perfect health; 0 = dead	Appropriateness for this cost-effectiveness analysis
Austin, 2010	Yes Patients who underwent pelvic	No SF-36 not a preference-based measure	No SF-36 version 2	Not applicable	Not appropriate

First author, year	Measured in patients	Values reflect public preferences using choice-based method	EQ-5D/other method used	Utility scale 1 = full or perfect health; 0 = dead	Appropriateness for this cost-effectiveness analysis
	exenteration for locally advanced, primary or recurrent rectal cancer				
AWMSG. 2010	Unclear	Unclear	Unclear Unspecified generic instrument	Unclear No utility estimates reported	N/A (no estimates reported)
Bennett, 2011	Yes Patients with mCRC treated with panitumumab in first- or second-line treatment	Yes Dolan (1997) UK tariff set used	Yes EQ-5D	Yes 1 = full health 0 = dead	Baseline estimates for patients starting second-line treatment are relevant to the "stable, non-progressive disease" health state
Best, 2010	Yes Patients (in the US) with Stage II-IV colon cancer	Yes (EQ-5D and direct TTO) and no (VAS for patients and community members)	Yes and other methods Health states valued by TTO were defined by the authors EQ-5D was used to categorise participant's current health	Yes For EQ-5D and TTO, 1 = full health, 0 = dead For EQ-5D VAS scores, 100 = full health, 0 = dead	EQ-5D data not appropriate for a mixture of patients receiving adjuvant therapy, in remission, and with metastatic disease TTO data for metastatic stable and metastatic progressive might be appropriate for the "stable, non-progressive disease" and "progressed" health states, respectively; however, details of health-state descriptions were not reported. Furthermore, as appears consistently in the evidence scores elicited from patient with specific health states are always better that scores assessed using hypothised health states. One must question the coherence of the Best data, when patients with the disease in question

First author, year	Measured in patients	Values reflect public preferences using choice-based method	EQ-5D/other method used	Utility scale 1 = full or perfect health; 0 = dead	Appropriateness for this cost-effectiveness analysis
					value their own health state much higher than they value hypothesised health states characteristic of the same disease.
Dranitsaris, 2011	No Oncology nurses	No Direct TTO but nurses not general public	No TTO	Yes 1 = full health, 0 = dead	Not appropriate
Dranitsaris, 2012	No Oncology nurses and pharmacists	No Direct TTO but staff not general public	No TTO	Yes 1 = full health, 0 = dead	Not appropriate
NICE, 2009	Yes Patients receiving first-line chemotherapy for mCRC with non-resectable metastases and an ECOG performance status ≤ 2	Unclear EQ-5D questionnaire, no valuation details	Yes EQ-5D	Yes 1 = full health, 0 = dead	Appropriate for the “stable, non-progressive disease” health state; however, there were only 37 evaluable questionnaires, patients were receiving cetuximab, and the trial population may not represent patients in routine clinical practice
NICE, 2010	Partially First-line chemotherapy and progressed disease estimates measured in patients with mCRC	Unclear First-line chemotherapy and progressed disease estimates valued using generic QoL instruments	Partially EQ-5D, expert opinion, and HUI	Yes 1 = full health, 0 = dead	First-line chemotherapy and disease progression estimates are appropriate for the “stable, non-progressive disease” and “progressed” health states respectively; however, patients were receiving cetuximab, and the trial population may not represent patients in routine clinical practice

First author, year	Measured in patients	Values reflect public preferences using choice-based method	EQ-5D/other method used	Utility scale 1 = full or perfect health; 0 = dead	Appropriateness for this cost-effectiveness analysis
NICE, 2011	Yes Patients with Stage III colon cancer and patients with metastatic breast cancer	Yes and No Direct TTO and VAS by patients and community members	Other method Health states were defined by the authors EQ-5D with VAS was used to categorise participant's current health	Yes and no 1 = full health, 0 = dead for utility and disutility estimates 100 = full health, 0 = dead for EQ-5D VAS scores	For data referenced to Best, 2010; see table entry one row above for NICE, 2010. Data referenced to Lloyd, 2006, are not appropriate because they were from breast cancer patients
NICE, 2012	Yes Patients with mCRC who had been previously treated with a fluoropyrimidine, irinotecan, and oxaliplatin or who had contraindications to these treatments	Unclear No details	Other method HUI	Yes 1 = full health, 0 = dead	Appropriate for the "stable, non-progressive disease" and "progressed" health states; however, HUI was used, patients were receiving cetuximab, and the trial population may not represent patients in routine clinical practice
Odom, 2011	Yes Patients with chemotherapy-refractory wild-type *KRAS* mCRC	Yes (US values) Shaw (2005) US tariff set	Yes EQ-5D	Yes 1 = full health, 0 = dead	Appropriate for the "progressed" health state; however, US value set was used and the trial population may not represent patients in routine clinical practice
Wiering, 2011	Yes Patients with colorectal liver metastases	Yes Dolan (1997) UK tariff set used	Yes EQ-5D	Yes 1 = full health, 0 = dead	Not appropriate; patients had resectable liver metastases without evidence of extrahepatic metastatic disease and had liver resection

AWMSG, All Wales Medicines Strategy Group; ECOG, Eastern Cooperative Oncology Group; EQ-5D, EuroQol 5-dimension health questionnaire; HUI, Health Utility Index; KRAS, Kirsten rat sarcoma viral oncogene homolog; mCRC, metastatic colorectal cancer; N/A, not applicable; NICE, National Institute for Health and Clinical Excellence; QoL, quality of life; SF-36, Short-Form 36-Item Health Survey; TTO, time tradeoff; UK, United Kingdom; US, United States; VAS, visual analogue scale.

An observational, non-interventional, cross-sectional study (mCRC utilities study) was performed by Sanofi to estimate utilities for patients with mCRC in routine clinical practice who would be eligible for treatment with aflibercept + FOLFIRI (according to the licensed indication) or had progressed to subsequent phases of disease. The study consisted of a brief chart review and a one-time interview-based administration of the EuroQol 5-dimension health questionnaire (EQ-5D-3L, EuroQol Group, 2012). The study was conducted in two sites in the Netherlands and two sites in the UK. Patients were eligible to participate if they met the following criteria: diagnosed with mCRC; aged 18 years or older; receiving second-line or subsequent lines of therapy (including BSC); received oxaliplatin but not irinotecan during first-line therapy; had ECOG PS scores of 0, 1, or 2 at the start of second-line therapy; and attended study sites for usual care visits over a 3-month period. For study purposes, second-line therapy was defined as a new line of therapy that was initiated due to disease progression diagnosis during first-line therapy.

The results from this study are not yet finalised as there are still some queries ongoing with the sites regarding patient numbers by health states, and there are limited data for the "second-line discontinued" state, however it is not anticipated that any additional data or substantial changes will occur for the stable and progressed states.

[redacted] Patients were assigned to one of the following health state groups:

- Stable currently receiving second-line therapy [redacted]
- Stable currently receiving third-line therapy or BSC following discontinuation from second-line therapy due to an adverse event [redacted]. Estimates from this group were not used in the model due to the small sample size.
- Progressed on or following second-line therapy and currently receiving third-line or subsequent lines of therapy or BSC [redacted]

Utility weights were estimated from the EQ-5D descriptive system data by application of the UK time trade-off tariffs (Dolan, 1997).

The utility weights from this study are applied in the model and are presented in Table B28 (section 7.4.9). Further details of this study are provided in appendix 12.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The utility estimates from the ASQoP study (section 7.4.3) are immature [redacted] is reasonably consistent with the range of estimates reported in the literature, with the exception of the study by Best (2010). Best (2010) reported time trade-off estimates for "metastatic stable" ranging from 0.40 to 0.54). The range of other published estimates relevant to the "stable non-progressive disease" health state was 0.73 to 0.81 (Bennett, 2011; NICE 2009; 2010; 2012). The value estimated by the Sanofi observational utility study (mCRC utilities study) also was within this range [redacted]

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Many adverse events are mild-to-moderate in nature and are effectively managed by dose reduction, dose delay or discontinuation of therapy. These events are expected to have a moderate and short-term impact on HRQL.

Grade 3-4 AEs, such as diarrhoea, stomatitis, fatigue, and vomiting (among the most common AEs in VELOUR) will have a marked impact on QoL. As discussed below to account for this (section 7.4.8), specific disutilities were applied in the model to account for AEs.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Utility estimates from the unpublished Sanofi observational utility study (mCRC utilities study, described in section 7.4.6) were applied in the model and are presented in Table B28.

These values were selected because they are EQ-5D utility estimates for the health states of interest that were collected in a sample of patients in routine clinical practice. The observational utility study applied simple selection criteria designed to recruit a study population consistent with the population that would be eligible to receive aflibercept + FOLFIRI in routine clinical practice (i.e., within the licensed indication) or were in subsequent phases of disease progression. As with other EQ-5D data reported by patients experiencing the health state (rather than proxies or estimates derived from theoretical health states) it is expected that these values provide the most accurate estimate of utility available in the population that would be eligible for treatment with aflibercept + FOLFIRI in clinical practice. The values observed in the observational utility study are reasonably consistent with the values found in the literature review reported directly from CRC patients (rather than from the community or proxies).

Table B28. **Summary of quality-of-life values for cost-effectiveness analysis**

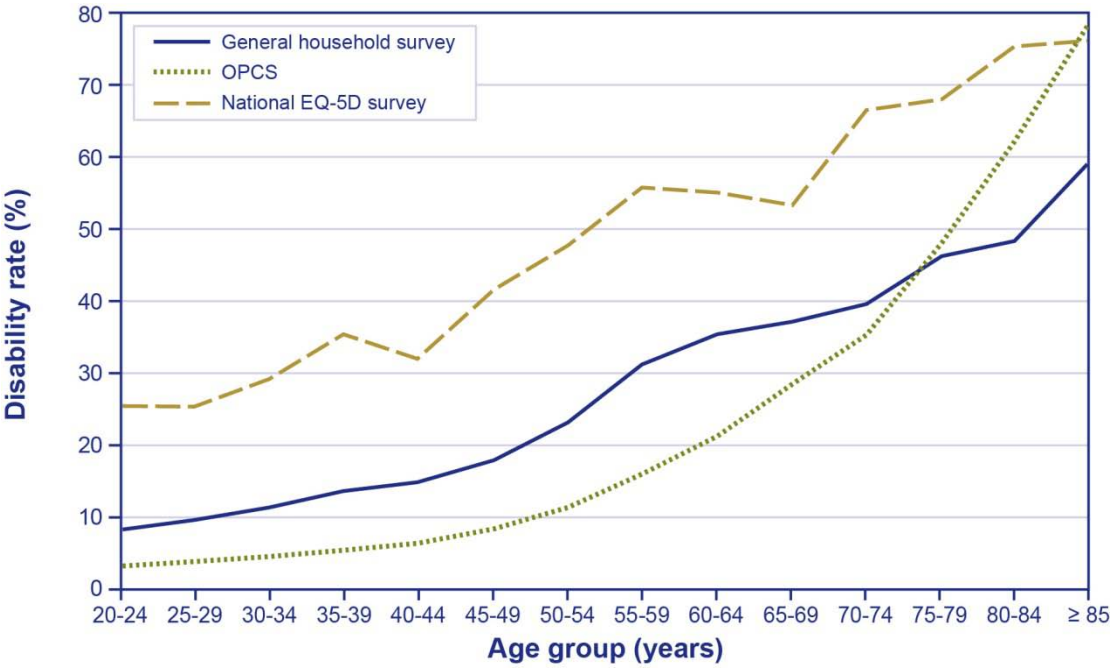
State	Mean utility value	Standard error	Reference in submission	Justification
Stable, on second-line treatment	[redacted]	[redacted]	Section 7.4.6	See text
Stable, discontinued second-line treatment	[redacted]	[redacted]	Section 7.4.6	See text
Progressed	[redacted]	[redacted]	Section 7.4.6	See text
Dead	0	NA	Assumption	

NA = not applicable.

The values found in this and in other studies in CRC are relatively high when considering the age and health status of the patients. When considering this, it is worthy of mention that the patients suitable for second-line chemotherapy must be fit enough to receive this. Despite their disease, they typically have a good performance status and reasonable HRQL and few comorbidities in addition to the disease itself. Those in a poorer state of health are unlikely to receive aggressive chemotherapy.

When viewed in the context of UK population norms, it should be noted that these UK norms are based on a sample from across society, which included a significant proportion of individuals reporting disability. Indeed, disability rates in the sample from which the UK general population norms were estimated were higher than in other national surveys. Rates (based on responses to the EQ-5D questionnaire) were 20% to 25% higher than rates in the general household survey for all age groups and about 30% to 40% higher than in the 1985 disability survey, until the age of 80 (Figure B-15) (Kind et al., 1998; 1999).

Disability rates from three national surveys (Kind et al., 1998)



EQ-5D, EuroQol 5-dimension health questionnaire; OPCS, The Office of Population Censuses and Surveys, now named the Office for National Statistics.

When considering the utility value for the progressed disease state, it is expected that patients in the progressive disease state would experience a decline in utility, particularly during the very end of life, in the terminal stage of their disease. Prior to this, further-line active treatment or best supportive care may provide additional control of the disease or symptoms respectively, helping to stabilise HRQL. The value from the utility study is likely to reflect such patients, who have progressive disease but whose symptoms are still being relatively well controlled either through additional lines of active therapy or best supportive care. It is obviously difficult both ethically and practically to provide EQ-5D data from those patients who are in the terminal phase of the disease. We expect therefore that the value for

the progressive disease state would not apply right through to the end of life, but that all patients would experience HRQL deterioration in the terminal phase of life, and that the duration of this would be independent of prior second-line therapy received.

Disutilities due to adverse events were based on the published literature, supplemented by clinical expert opinion. Because published data specific to patients with CRC who were experiencing specific adverse events were not identified, it was assumed that the disutility associated with adverse events was independent of the cancer type. For example, the disutility associated with diarrhoea was the same irrespective of the type of cancer the patient was experiencing. Table B29 presents the disutility values applied in the model.

Table B29. **Adverse event disutilities**

Adverse event	Disutility	Justification (source)
Diarrhoea	–0.103	Grade 3/4; utility value for diarrhoea and vomiting combined (Lloyd et al., 2006, Table 3)
Hypertension	–0.069	Assumption, smallest decrement of the range of values for other AEs
Fatigue	–0.115	Grade 3/4 (Lloyd et al., 2006, Table 2)
Stomatitis	–0.151	Grade 3/4 (Lloyd et al., 2006, Table 3)
Abdominal pain	–0.069	(Doyle et al., 2008)
Vomiting	–0.103	Grade 3/4; utility value for diarrhoea and vomiting (combined) (Lloyd et al., 2006, Table 3)
Dehydration	–0.103	Assumed the same as vomiting
Decreased appetite	–0.069	Assumption; smallest decrement of the range of values for other AEs
Nausea	–0.048	Grade 3/4 nausea and vomiting (Nafees et al., 2008)
Neuropathy peripheral	–0.116	Assumed same as for hand-foot syndrome (Lloyd et al., 2006)
Infections	–0.195	(Tolley et al., 2010)
Hand-foot syndrome	–0.116	Grade 3/4 (Lloyd et al., 2006, Table 3)
Gastrointestinal perforation	–0.195	Assumed highest in the range
Haemorrhage	–0.195	Assumption; largest decrement of the range of values for other AEs
Febrile neutropaenia	–0.15	Grade 3/4 (Lloyd et al., 2006, Table 3)
Neutropaenia	–0.09	Grade 3/4 (Nafees et al., 2008)
Asthenia	–0.115	Assumed same as fatigue

AE, adverse event.

To calculate the overall disutility experienced by a patient on a given second-line treatment, the disutilities presented above were weighted with the distribution of the specific adverse events and the mean duration of the adverse events (assumed to equal the length of

treatment in years) estimated from the VELOUR trial (Table B30). This has the effect of assuming that disutilities due to adverse events are additive.

Table B30. **Distribution and duration of adverse events experienced in the VELOUR trial**

AE	Distribution of AEs, %[a]		Mean length of treatment (years)
	Aflibercept + FOLFIRI	FOLFIRI	
Diarrhoea	15.6	10.6	0.12
Hypertension	16.5	2.1	0.16
Fatigue	10.2	10.6	0.42
Stomatitis	9.4	6.1	0.21
Abdominal pain	2.8	2.9	0.15
Vomiting	1.9	5.2	0.02
Dehydration	3.0	1.7	0.03
Decreased appetite	2.4	2.5	0.38
Nausea	1.1	4.2	0.04
Peripheral neuropathy	0.7	0.6	0.44
Infections	0.5	1.0	0.11
Hand-foot syndrome	1.8	0.6	0.74
Gastrointestinal perforation	0.3	0.4	1.10
Haemorrhage	2.2	2.1	0.05
Febrile neutropaenia	3.0	2.1	0.02
Neutropaenia	25.2	43.2	0.03
Asthenia	3.4	4.0	0.44

AE, adverse event; FOLFIRI, 5-fluorouracil/leucovorin/irinotecan.

[a] The proportion of all AEs by type, calculated as the number of new cases of a given AE divided by the total number of all new AE cases.

Source: Sanofi data on file, 2011.

The average disutility per adverse event was –0.0127 for aflibercept + FOLFIRI and –0.0108 for FOLFIRI. The average disutilities were multiplied by the per-cycle probability of an adverse event occurring. Adverse event rates described in the previous section were transformed into cycle probabilities using the following formula:

$$1 - \exp(-\text{mean rate}).$$

Utility weights and disutilities were sampled from beta distributions in the probabilistic sensitivity analysis.

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- The criteria for selecting the experts
- The number of experts approached
- The number of experts who participated
- Declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- The background information provided and its consistency with the totality of the evidence provided in the submission
- The method used to collect the opinions
- The medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- The questions asked
- Whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

A clinical and economic advisory board reviewed the model parameters alongside the model structure and advised on their appropriateness. Three advisory board meetings were held, one during the model design phase and two after completion of the model.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

A description of patient experience in each health state in terms of HRQL is presented in Table B31.

Table B31. **Health-related quality of life experienced in each health state**

Health state	Description of HRQL experienced
1. Stable, non-progressive disease, on second-line treatment	Patients have mCRC and have progressed after first-line treatment with an oxaliplatin-containing regimen. Their disease is currently stable. In the model, patients are assumed to have the utility associated with stable disease. Patients are receiving second-line chemotherapy and may experience AEs. Most AEs are mild to moderate and short term in nature and are managed by dose reduction or delay; these are likely to have a minor impact on HRQL. Some AEs may be severe, long term, and/or require treatment and/or hospitalisation; these events may have a substantial impact on HRQL for the duration of the event. In the model, disutilities are applied for severe AEs for the duration of the AE.
2. Stable, non-progressive disease,	Patients have mCRC and have progressed after first-line treatment with an oxaliplatin-containing regimen and subsequently discontinued

[5] Adapted from Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee; 2008.

Health state	Description of HRQL experienced
discontinued second-line treatment	second-line treatment. Their disease is currently stable. In the model, patients are assumed to have the utility associated with stable disease. AEs associated with second-line treatment may persist. Patients may receive subsequent lines of therapy and may experience AEs. However, due to the lack of data available for AEs persisting after second-line treatment or AEs associated with subsequent lines of therapy, no disutilities due to AEs are applied in the model.
3. Progressed	Patients have mCRC and have progressed after second-line treatment. Their condition is likely to be stable, with any symptoms managed accordingly. Patients progressing to terminal illness experience poor quality of life close to death. In the model, patients are assumed to have the utility associated with progressive disease.
4. Dead	Not applicable
AE, adverse event; HRQL, health-related quality of life; mCRC, metastatic colorectal cancer.	

7.4.12 *Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?*

No health effects were excluded.

7.4.13 *If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?*

No baseline quality of life was assumed; utility values for each health state were applied.

7.4.14 *Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.*

HRQL within each health state is assumed to be constant over time. The HRQL of the population changes over time as patients progress through the health states.

7.4.15 *Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.*

No HRQL data were collected in the VELOUR trial; utilities were not mapped from data collected in the VELOUR trial.

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 *Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.*

NHS Reference Costs and Unit Costs of Health and Social Care are presented in Table B32 for medical visits and Table B33 for hospitalisations. Costs for Personal and Social Services, laboratory tests, imaging, drugs and procedures, inpatient AE treatment, medication and IV fluids are presented in appendix 15.

Table B32. **NHS reference costs: medical visits**

Resource item	Unit	Code	Description	Unit cost (£)	Source/ notes
Chemotherapy administration	Per administration visit	SB14Z	Deliver chemotherapy	331.36	NHSRC, 2011-2012
Oncologist	Per contact	370	Medical oncology: follow-up attendance non-admitted face to face	123.71	NHSRC, 2011-2012
Nurse	Per contact	10.6	Nurse (GP practice): per hour	35.00	PSSRU, 2012
Pain specialist	Per contact	191	Pain management: follow-up attendance non-admitted face to face	114.63	NHSRC, 2011-2012
Palliative care team	Per consultation	315	Palliative medicine: follow-up attendance non-admitted face to face	270.05	NHSRC, 2011-2012
Palliative care team	Per consultation over the telephone	—	The average cost of a contact with one nurse advisor or health information advisor	21.02	NHS Direct
GP	Per contact	10.8b	GP: per clinic consultation lasting 17.2 minutes	48.00	PSSRU, 2012
Dietician visit	Per contact	654A	Dietetics total contacts: adult (19 and over) follow-up	93.00	NHSRC, 2011-2012
Cardiologist	Per contact	320	Cardiology: follow-up attendance	121.57	NHSRC, 2011-2012
Specialist nurse	Per contact	10.4	Nurse specialist (community): per hour	43.00	PSSRU, 2012
District nurse	Per patient-related hour	10.1	Community nurse (district nurse): per hour of patient-related work	51.00	PSSRU 2012

GP, general practitioner; NHS, National Health Service; NHSRC, National Schedule of Reference Costs; PSSRU, Personal Social Services Research Unit.

[a] In the model, an additional 15 minutes of nurse time (based on clinical opinion) was added for the irinotecan-based regimens, to account for the removal of the infusion pump that was needed for irinotecan administration. The additional cost was £13.75 (NHSRC, 2011).

Table B33. **NHS reference costs and payment by results tariffs: hospitalisations**

Resource item	Unit	Code	Unit cost (£)	Description	Source	Activity	LOS
General ward	Day	FZ46A	3,443.66	Malignant large intestinal disorders with LOS 2 days or more with major CC: NHS Trusts and PCTs combined nonelective inpatient (long stay) HRG data	NHSRC, 2011-2012	7,174	10.32
	Day	FZ46B	2,311.43	Malignant large intestinal disorders with LOS 2 days or more without major CC: NHS Trusts and PCTs combined nonelective inpatient (long stay) HRG data	NHSRC, 2011-2012	3,505	5.94
	Day	FZ46C	1493.03	Malignant large intestinal disorders with LOS 1 day or less: NHS Trusts and PCTs combined nonelective inpatient (long stay) HRG data	NHSRC, 2011-2012	437	3.83
	Day	FZ46A	728.10	Malignant large intestinal disorders with LOS 2 days or more with major CC: NHS Trusts and PCTs combined nonelective inpatient (short stay) HRG data	NHSRC, 2011-2012	28	NA
	Day	FZ46A	229.64	Malignant large intestinal disorders with LOS 2 days or more with major CC: NHS Trusts and PCTs combined nonelective inpatient (long stay-excess bed days) HRG data	NHSRC, 2011-2012	NA	NA
	Day	FZ46B	355.52	Malignant large intestinal disorders with LOS 2 days or more without major CC: NHS Trusts and PCTs combined nonelective inpatient (short stay) HRG data	NHSRC, 2011-2012	15	NA
	Day	FZ46B	238.57	Malignant large intestinal disorders with LOS 2 days or more without major CC: NHS Trusts and PCTs combined nonelective inpatient (long stay-excess bed days) HRG data	NHSRC, 2011-2012	NA	NA
	Day	FZ46C	527.27	Malignant large intestinal disorders with LOS 1 day or less: NHS Trusts and PCTs combined nonelective inpatient (short stay) HRG data	NHSRC, 2011-2012	4,523	NA
ICU	Day	7.1	654	Hospital costs: Intensive care adult (cost per bed day)	PSSRU, 2012	-	-
A&E	Admission	7.1	146.00	A&E treatments leading to admission	PSSRU, 2012	-	-

Resource item	Unit	Code	Unit cost (£)	Description	Source	Activity	LOS
admission							

A&E, accidents and emergency; CC, colon cancer; HRG, Healthcare Research Group; ICU, intensive care unit; LOS, length of stay; NA, not available; NHS, National Health Service; NHSRC, National Schedule of Reference Costs; PCT, primary care trust; PSSRU, Personal Social Services Research.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

NHS Reference costs in combination with other sources of unit costs (e.g., Unit Costs of Health and Social Care, drug prices) and resource use estimates are appropriate for the analysis.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- *Country of study*
- *Date of study*
- *Applicability to UK clinical practice*
- *Cost valuations used in study*
- *Costs for use in economic analysis*
- *Technology costs.*

A systematic review was performed to identify resource use and cost studies relevant to this appraisal. This review was performed as part of a wider systematic review described previously (section 7.1) which also aimed to identify cost-effectiveness studies of aflibercept, and utility estimates relevant to the appraisal. Full details of the systematic review are included in appendix 10.

The searches, inclusion criteria and exclusion criteria were designed to identify the following:

- Resource use and/or cost studies for mCRC
- Resource use and/or cost studies for adverse events related to second-line treatments in patients with mCRC (diarrhoea, hypertension, fatigue, stomatitis, abdominal pain, vomiting, dehydration, decreased appetite, nausea, neuropathy, infections, hand-foot syndrome, gastrointestinal perforation, haemorrhage, and febrile neutropaenia).

The following study types were excluded:

- Studies reporting costs for countries other than the United Kingdom
- Studies reporting resource use for countries other than the United Kingdom, unless no UK-specific data were available
- Studies that did not report primary data (i.e., estimates were referenced to other reports); in this event, the original reports of the referenced studies were screened for inclusion in the review and included where appropriate

Figure B-9 in section 7.1 presents the results in a PRISMA flow chart. Two studies were identified. In addition, resource use and cost estimates were reported in the documentation for three HTAs. The studies are summarised in Table B34. One further resource use study was performed by Sanofi (UK mCRC resource use study). This study is not yet published and is summarised in the text following Table B34.

Table B34. **Resource use and cost studies identified by the systematic review**

First author (year)	Description of available data	Details of methods[a]	Country, data year, cost year	Applicability to this evaluation
AWMSG, 2011	Company-reported total costs of treatment with XELOX, FOLFOX6, or FOLFOX4 per patient. Drug regimen costs for capecitabine, folinic acid, and oxaliplatin. Central venous access device, pharmacy preparation, and administration costs. Grade 3/4 AE costs. Welsh budget-impact estimates.	Submission is based on an indirect comparison of XELOX and FOLFOX4. This indirect analysis includes the NO16968 (XELOXA) trial and the MOSAIC trial. The company submission describes a cost-minimisation analysis of the XELOX regimen compared with the FOLFOX4 and FOLFOX6 regimens as adjuvant treatment after surgery in patients with Stage III colon cancer.	Wales, NR, NR	Not applicable Study reports aggregate costs for XELOX and FOLFOX regimens and AEs associated with these regimens No unit costs that could be used in this evaluation were reported
Faiz, 2011	LOS for patients undergoing elective colonic and rectal resection procedures for malignancy from 1996-2006.	Study is designed to predict prolonged stay and readmissions in NHS hospitals. Data were collected from the Hospital Episode Statistics data set. Procedures were assigned according to OPCS-4 codes in the database and grouped into the following procedure categories: proximal colectomy, distal colectomy, total colectomy, anterior resection with stoma, anterior resection without stoma, and abdominoperineal excision.	UK, 1996-2006, cost-year NR	Not applicable Data reported related to the LOS for patients undergoing resection of colorectal cancer

First author (year)	Description of available data	Details of methods[a]	Country, data year, cost year	Applicability to this evaluation
NICE, 2011	Drug administration cost per cycle Cost of management for febrile neutropaenia and grade 3/4 diarrhoea Supportive care costs	Taken from the NHS Reference Costs 2008-2009 (SB12Z/SB13Z) NHS reference costs 2008-2009 (FZ45C) and PbR tariff 2010-2011 (PA45Z) PSSRU, 2009; PbR tariff, 2010-2011 (WF01B); and NHS reference costs 2008-2009 (FZ48B)	UK, 2009, 2009	Yes
NICE, 2012	Drug administration costs *KRAS* testing costs AE costs Medical management costs Deterministic results of PenTAG and Merck Serono cost-effectiveness models	Analysis of Merck Serono cost-effectiveness model submitted to NICE as part of TA242 PenTAG economic model based on clinical and economic systematic reviews	UK, 2008-2011, 2012	Yes
Shabaruddin, 2010b	Mean days of treatment, mean cycles, patients with neutropaenia, resource use, and cost associated with irinotecan chemotherapy (FOLFIRI, modified de Gramont) for colorectal cancer	A patient-level, bottom-up, micro-costing study was used to identify resource use from the hospital perspective. Resource use data were collected from the medical records of patients recruited at The Christie Hospital, a UK tertiary-care oncology centre. The time horizon used started from the beginning until the end of irinotecan chemotherapy	UK, 2009, 2009	Yes Disaggregated data suitable for model inputs were not reported. Overall cost of FOLFIRI regimen (UK, 2009) may be compared with model results (mean cost per patient was £12,474 [95% CI, £11,233-£13,715, median £13,308, range £3,024-£21,276] over an average treatment duration of 5 months (9 cycles)

First author (year)	Description of available data	Details of methods[a]	Country, data year, cost year	Applicability to this evaluation

AE, adverse event; AWMSG, All Wales Medicines Strategy Group; CI, confidence interval; FOLFIRI, 5-fluorouracil/leucovorin/irinotecan; FOLFOX4, leucovorin 200 mg/m^2 as a 2-hour infusion, followed by bolus 5-fluorouracil 400 mg/m^2 and a 22-hour infusion of 5-fluorouracil 600 mg/m^2 for 2 consecutive days every 14 days, plus a 2-hour infusion of 85 mg/m^2 of oxaliplatin on day 1, given simultaneously with leucovorin; FOLFOX6, oxaliplatin (day 1, 100 mg/m^2) with leucovorin (400 mg/m^2 [racemic] or 200 mg/m^2 [L-form]) plus 5-fluorouracil (400 mg/m^2 bolus plus 2,400 mg/m^2 as a 46-hour continuous infusion) every 2 weeks; KRAS, Kirsten rat sarcoma viral oncogene homolog; LOS, length of stay; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; NR, not reported; OPCS-4, Statistical Classification of Surgical Operations version 4; PbR, payment by results; PenTAG, Peninsula Technology Assessment Group, PSSRU, Personal Social Services Research; UK, United Kingdom; XELOX, capecitabine and oxaliplatin.

[a] Including patient population, treatments, type of study, and cost valuations used (where applicable).

Sanofi performed a retrospective observational study in the UK, to describe the NHS resource use associated with the management of patients with mCRC in the hospital setting (UK mCRC resource use study - unpublished). The study took place in [redacted] and included patients who received an irinotecan-based chemotherapy regimen, following prior treatment with an oxaliplatin-based regimen. All data were sourced retrospectively from eligible patients' medical notes and electronic hospital systems by the routine clinical care team. Chemotherapy treatment information was captured from the start of chemotherapy treatment for CRC. Resource use data were captured from the start of irinotecan-based chemotherapy for mCRC to the date of data collection or death, whichever occurred first. Resource use in the end-of-life period [redacted], because this resource use is incurred by all patients in the model (and is therefore equal for the two treatment cohorts), and because inclusion of the higher costs in the end-of-life period would result in overestimation of the average per-cycle management cost. The end-of-life period was defined as [redacted] on the basis of resource use study data, which demonstrated a marked increase in the incidence of hospitalisations during the last [redacted] (details provided in appendix 15).

Resource use data were summarised for the following three phases of disease, which were aligned with the model health states:

- Stable, on second-line treatment (patients receiving FOLFIRI): [redacted]
- Stable, discontinued second-line treatment: [redacted] for active treatment and BSC, respectively
- Progressed: [redacted] for active treatment and best supportive care, respectively

Resource use per 2-week period was summarised separately for patients receiving active therapy and those receiving BSC (number and percentage of patients using the resource, mean number used, and standard deviation). Unit costs were applied to estimate total management costs per 2-week model cycle. For the probabilistic sensitivity analysis, the mean for each resource use item was sampled from a gamma distribution. Further details of the study are provided in appendix 15). The mean management costs for each health state are presented in Table B36 (section 7.5.6).

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- *The criteria for selecting the experts*
- *The number of experts approached*
- *The number of experts who participated*
- *Declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought*

[6] Adapted from Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee; 2008.

- *The background information provided and its consistency with the totality of the evidence provided in the submission*
- *The method used to collect the opinions*
- *The medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)*
- *The questions asked*

Community-based care and personal and social care were estimated via a survey of UK clinical oncology experts. The experts were selected on the basis of knowledge and experience in mCRC, knowledge and experience in health economics, and availability. Fifteen experts were approached, and six participated. No declaration of conflict of interest was requested, because only disease-specific data, not treatment-specific data, were discussed.

The experts were asked to complete a resource use questionnaire which was developed to obtain all relevant data regarding the management of patients with mCRC and adverse events after failure of first-line treatment in England and Wales. The questions aimed to elicit the average treatment practices of each oncologist.

The community care and personal and social care data were used in the model. Questions related to these data focussed on the following:

- Visits due to mCRC in community-based health care settings by treatment arm and by therapy.
- One-off costs at time of regimen change:, number of physician visits in the community based setting, proportion of patients receiving different types of laboratory tests separately for patients who discontinued second line treatment and those who are in the progressive disease.
- Resource use associated with AEs: GP visits.
- Personal and social services: proportion of patients receiving care, frequency of residential care, day care, home care and hospice care, proportion of services funded by NHS.

End of life resource use was not included in the questionnaire since every patient, irrespective of the comparator, has to pass through this type of care and therefore no incremental difference in costs and benefits are expected. In consequence, this end of life care was not incorporated in the model.

The response from each of the six physicians was collated and synthesised using summary statistics (median, mean, standard deviation).

A clinical and economic advisory board reviewed the model parameters alongside the model structure and advised on their appropriateness. Three advisory board meetings were held, one during the model design phase and two after completion of the model.

Intervention and comparators' costs

7.5.5 *Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.*

Second-line drug costs were calculated outside of the patient flow of the model and were based on the treatment duration observed in the VELOUR trial. The cost calculations for each treatment were based on the following general principles:

- **Mean dose administered.** Doses are adjusted for patients' body weight and/or body surface area (BSA) (see section 7.2.7). Dose reductions may occur (e.g., due to toxicity). The mean dose per administration (per kg or m^2) was estimated for each drug from the VELOUR trial data.
- **Drug cost per administration.** In the base-case analysis, the cost of drug per dose administered was calculated assuming that unused drug in opened vials is discarded[7]. In this analysis, the weight and BSA distributions of the Western European population in the VELOUR trial were used to estimate the proportion of patients receiving each vial combination. Sensitivity analyses were performed for two additional scenarios:

  – No drug wastage (costs were calculated based on the mean dose and the unit cost per mg)

  – Drug wastage as before; however, for patients requiring an amount of drug that was less than 5% higher than the amount contained in the nearest number of whole vials, the dose was "stepped down" to the nearest number of whole vials. This is referred to as the "5% step-down" scenario. Dose rounding to within 5% of calculated dose has been considered not to have any significant clinical effect on either response or toxicity (Dooley et al., 2004). Clinical experts have verified that it is routine to apply rounding of doses in oncology pharmacies. Although the rounding mechanism that would apply for aflibercept is unknown, clinical experts have commented that a 5% rounding is likely to be conservative (Advisory Board November, 2012).
- **Duration of treatment.** The mean duration of treatment[8] for aflibercept + FOLFIRI and FOLFIRI were taken from the VELOUR trial. In the subgroup analyses, data specific to the individual subgroup were applied.

Drug cost per 2-week model cycle. The drug cost per model cycle took into account dose delays (e.g., due to toxicity) by using estimates of the mean number of administrations per 2-

[7] A simplifying assumption was made that the cost of discarded 5-FU and leucovorin is negligible in comparison with the total treatment costs as these drugs are relatively very cheap, and calculations are very complex due to the number of vial sizes available. Therefore, cost calculations for 5-FU and leucovorin assume no wastage.

[8] The duration of treatment was defined as the overall treatment duration of the combination, i.e., from the first day of the cycle, where any part of the combination was first administered, to the last day of the cycle where the last component was administered.

week period observed in the VELOUR trial. This was calculated as the total number of administrations (for each drug individually) divided by the total duration of treatment for the regimen (in 2-week model cycles). The costs for each intervention are presented in Table B35. The mean drug cost per model cycle was applied in the model in each cycle that the patient continued second-line treatment[9].

The cost of disease monitoring, imaging and laboratory tests were assumed to be the same for all interventions and were included in the cost of disease management for the "Stable, non-progressive disease, on second-line treatment" health state (see section 7.5.6).

Table B35. **Costs associated with the technologies in the model**

Items	Aflibercept + FOLFIRI	FOLFIRI
Scheduled dose		
Aflibercept	4 mg/kg	-
Irinotecan	180 mg/m^2	180 mg/m^2
Leucovorin	400 mg/m^2	400 mg/m^2
5-FU	400 + 2,400 mg/m^2	400 + 2,400 mg/m^2
Source	VELOUR trial	VELOUR trial
Administered dose		
Aflibercept	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]
Leucovorin	[redacted]	[redacted]
5-FU	[redacted]	[redacted]
Source	VELOUR trial, WE	VELOUR trial, WE
Drug cost (per model cycle): base case (includes wastage)[a]	[redacted]	[redacted]
Drug cost (per model cycle): no wastage[a]	[redacted]	[redacted]
Drug cost (per model cycle: 5% step-down[a]	[redacted]	[redacted]
Mean number of administrations		
Aflibercept	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]
Leucovorin	[redacted]	[redacted]
5-FU	[redacted]	[redacted]
Source	VELOUR trial	VELOUR trial
Mean duration of	[redacted]	[redacted]

[9] In cases where the mean number of model cycles that treatment was continued was not an integer (e.g., the mean duration of treatment was [redacted]), the fraction of treatment in the last cycle of treatment was included (i.e., in this example, the drug cost in the last cycle of treatment was calculated as 0.1 times the cost per cycle)

Items	Aflibercept + FOLFIRI	FOLFIRI
treatment (model cycles)[b]		
Source	VELOUR trial	VELOUR trial
Total cost (base case)	[redacted]	[redacted]

FU, fluorouracil; FOLFIRI, fluorouracil/leucovorin/irinotecan; VELOUR, Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Colorectal Cancer After Failure of an Oxaliplatin Based Regimen; WE, Western European population of the VELOUR trial**.**

[a] Mean cost per 2-week model cycle. Calculations include dose adjustment for patient weight and BSA, dose reductions and dose delays (e.g., for toxicity).

[b] The duration of treatment was defined as the overall treatment duration of the combination, i.e., from the first day of the cycle, where any part of the combination was first administered, to the last day of the cycle where the last component was administered.

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

Management costs for patients in each of the model health states are presented in Table B36. Estimates were calculated by combining resource use estimates collected in the observational study performed by Sanofi (section 7.5.3) and the physician survey (section 7.5.4) and unit costs. Responses from the six physicians were synthesised by calculating the median of all responses before application of unit costs. Median values were used due to clearly skewed data. Management costs included supportive medications, physician and nurse visits (hospital and community), imaging, laboratory tests, hospitalisations, palliative care. and personal and social care.

The cost of subsequent lines of chemotherapy was applied separately (see section 7.5.8). End-of-life care [redacted]) was not included in the "Progressed" health state because every patient is assumed to receive this prior to death whichever treatment arm they are in. End of life care was not included in the model.

Table B36. **List of health states and associated costs in the economic model**

Health state	Cost
Stable, non-progressive disease, on second-line treatment (per cycle)	[redacted]
Stable, non-progressive disease, discontinued second-line treatment	[redacted]
One-off cost of regimen change on entering health state	[redacted]
Active treatment (lump sum)	[redacted]
Best supportive care (per cycle)	[redacted]
Progressed	[redacted]
One-off cost of regimen change on entering health state	[redacted]

Active treatment (lump sum)	[redacted]
Best supportive care (per cycle)	[redacted]
[redacted]	

Adverse-event costs

7.5.7 *Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.*

The costs for AEs are presented in Table B37. Costs for diarrhoea and febrile neutropaenia were based on NHS reference costs. The remaining estimates were calculated by combining resource use estimates collected in the physician survey (section 7.5.4) and unit costs . Responses from the six physicians were synthesised by calculating the median of all responses before application of unit costs.

Table B37. **List of adverse events and summary of costs included in the economic model**

Adverse event	Cost (£)	Source
Diarrhoea	475	NHSRC, 2011-2012; FZ45C Non-Malignant Large Intestinal Disorders, with length of stay 1 day or less
Hypertension	759	Physician survey for RU data applied to unit costs
Fatigue	90	Physician survey for RU data applied to unit costs
Stomatitis	929	Physician survey for RU data applied to unit costs
Abdominal pain	1,066	Physician survey for RU data applied to unit costs
Vomiting	360	Physician survey for RU data applied to unit costs
Dehydration	672	Physician survey for RU data applied to unit costs
Decreased appetite	0	Physician survey for RU data applied to unit costs
Nausea	310	Physician survey for RU data applied to unit costs
Neuropathy peripheral	288	Physician survey for RU data applied to unit costs
Infections	328	Physician survey for RU data applied to unit costs
Hand-foot syndrome	338	Physician survey for RU data applied to unit costs
Gastrointestinal perforation	469	Physician survey for RU data applied to unit costs

Haemorrhage	576	Physician survey for RU data applied to unit costs
Febrile neutropaenia	5,675	PbR Tariff, 2011-2012; PA45Z Febrile Neutropaenia with Malignancy
Neutropaenia	1,586	Physician survey
Asthenia	263	Physician survey

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

Drug Cost of Subsequent Therapies

The following costs of subsequent drug therapies were included:

- Therapies after discontinuation of second-line therapy but before disease progression (pre-progression subsequent therapies)
- Therapies after disease progression (post-progression subsequent therapies).

Information about subsequent therapies were collected in the VELOUR trial but were limited to drugs and classes. The distribution, dosage, and treatment duration for subsequent therapies were estimated from the Sanofi UK retrospective observational resource-use study (UK mCRC resource use study; sections 7.5.3 and appendix 15). These were combined with unit costs to estimate the cost of therapy. The patterns of subsequent therapies pre- and post-disease progression were assumed to be independent of the type of second-line treatment (based on expert opinion).

The patterns of subsequent therapy and their costs are presented in Table B38.

Table B38. **Pattern of subsequent drug therapy**

Therapy	Pre-progression	Post-progression
Patients receiving each regimen, %		
Active therapy	[redacted]	[redacted]
Best supportive care	[redacted]	[redacted]
Total cost of subsequent therapy,£ [a]	[redacted]	[redacted]
Chemotherapy drugs[a]	[redacted]	[redacted]
Chemotherapy administration[a]	[redacted]	[redacted]
Cost of best supportive care (per cycle)[b]	[redacted]	[redacted]

5-FU, 5-fluorouracil; FOLFIRI, 5 fluorouracil/leucovorin/irinotecan; FOLFOX, folinic acid plus fluorouracil plus oxaliplatin; NR, not reported.

Note: Reference in the submission: Sanofi UK retrospective observational study (UK mCRC resource use study; sections 7.5.3 and appendix 15).

[a] Average one-off cost applied for all patients (accounts for proportion of patients receiving no subsequent therapy).

[b] Applied for patients receiving best supportive care only ([redacted]

7.6 Sensitivity analysis

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

Uncertainty in the selection of the parametric survival functions was investigated by applying alternative functions. In addition, because all patients reached the PFS endpoint within the VELOUR trial follow-up, Kaplan-Meier data for PFS were applied directly in sensitivity analysis.

Uncertainty as to the relative clinical relevance of the two definitions of disease-free survival in the VELOUR trial (IRC and investigator assessment) with respect to detection of disease progression in routine clinical practice was investigated by applying data for each definition in sensitivity analysis.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

One-way deterministic sensitivity analyses were performed for all major model variables. Parameters were set to their extreme values [redacted] of the base case) one-by-one, in order to see their independent effects on the results.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA was performed using 5,000 simulations. The distributions for key parameters are summarised in section 7.3.6.

7.7 Results

Clinical outcomes from the model

7.7.1 *For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.*

The results from the model are broadly similar to those from the clinical trial. The largest difference is observed for PFS for the FOLFIRI arm, which may be due to the fact that there were some discrepancies in fitting the Weibull function to PFS but in the absence of strong justification it was considered preferable to choose this to be consistent with the aflibercept arm. The result is that PFS is greater in the model than in the trial for the FOLFIRI arm. Other reasons for differences (applying to all values) are likely to be due to the fact that the model is based on parametric functions rather than on K-M data, and probabilities are applied on a cycle-by-cycle basis.

Table B39. **Summary of model results compared with clinical data**

Treatment group and outcome	VELOUR	Model[a]
Aflibercept + FOLFIRI		
PFS (median, months)[b]	6.90	[redacted]
Post-progression survival	NA	[redacted]
OS (median, months)	13.50	[redacted]
FOLFIRI		[redacted]
PFS (median, months)[b]	4.67	[redacted]
Post-progression survival	NA	[redacted]
OS (median, months)	12.06	[redacted]
Adverse events	Numbers of adverse events observed in the VELOUR trial were applied directly in the model (see Table B30)	

FOLFIRI, 5 fluorouracil/leucovorin/irinotecan; NA, not available; OS, overall survival; PFS, progression-free survival.

[a] Undiscounted estimates.

[b] Independent Review Committee judgement of disease progression.

7.7.2 *Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.*

The percentage of the cohort in each health state over time is presented for the aflibercept + FOLFIRI cohort and for the FOLFIRI cohort in Figure B-15 and Figure B-16, respectively.

Figure B-15. [redacted]

[redacted]

[redacted]

Figure B-16. [redacted]

[redacted]

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The accrual of life-years and QALYs over time in each cohort is presented in Figure B-17 and Figure B-18.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.7.4 *Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:*

Estimates of life-years, QALYs, and costs accrued by health state are in Table B40.

Table B40. **Model outputs by clinical outcomes**

Outcome	LY[a]	QALY[a]	Cost (£)[a]
Aflibercept + FOLFIRI cohort			
PFS[b]	[redacted]	[redacted]	[redacted]
Post-progression survival	[redacted]	[redacted]	[redacted]
OS	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
FOLFIRI cohort	[redacted]	[redacted]	[redacted]
PFS[b]	[redacted]	[redacted]	[redacted]
Post-progression survival	[redacted]	[redacted]	[redacted]
OS	[redacted]	[redacted]	[redacted]

Outcome	LY[a]	QALY[a]	Cost (£)[a]
Adverse events	[redacted]	[redacted]	[redacted]

[a] Undiscounted estimates.

[b] Outcomes within the "Stable, non-progressive disease" health state, including "On second-line treatment" and "discontinued second-line treatment" substates.

[c] Any deaths due to adverse events were included in the OS endpoint; therefore, the model did not estimate the probability of death from individual adverse events. LYs lost due to adverse events therefore cannot be disaggregated.

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost.

Table B41. **Summary of quality-adjusted life-year gain by health state**

Health state	QALY: aflibercept + FOLFIRI	QALY: FOLFIRI	Increment	Absolute increment	% absolute increment
Stable, non-progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table B42. **Summary of costs by health state**

Health state	Cost (£): aflibercept + FOLFIRI	Cost (£): FOLFIRI	Increment (£)	Absolute increment (£)	% absolute increment
Stable, non-progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table B43. **Summary of predicted resource use by category of cost**

Item	Cost (£): aflibercept + FOLFIRI	Cost (£): FOLFIRI	Increment (£)	Absolute increment (£)	% absolute increment
Drug and administration costs for second-line treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other pre-progression costs					
Drug costs for subsequent lines of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs for subsequent lines of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regimen change and progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression costs					
Drug costs post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FOLFIRI, 5 fluorouracil/leucovorin/irinotecan.

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

The base-case analysis results are presented in Table B44.

Table B44. **Base-case results**

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
FOLFIRI[b]	[redacted]	[redacted]	[redacted]	—	—	—	—	—
Aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]	8,816	0.3378	0.2429	36,294	36,294

5-FU, 5-fluorouracil; FOLFIRI, 5 fluorouracil/leucovorin/irinotecan; ICER, incremental cost-effectiveness ratio; IRC, independent review committee; LYG, life-years gained; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life-years.

[a] Costs and outcomes are discounted at 3.5% per annum. The analysis time-horizon was 15 years. Survival functions for PFS and OS were the Weibull (IRC) and log-logistic functions respectively (fitted to each treatment group separately). The cost of aflibercept and irinotecan assumed that unused drug in opened vials is discarded (no step-down to the nearest number of whole vials was assumed); the cost of wasted leucovorin and 5-FU was assumed to be negligible and similar for both treatment groups.

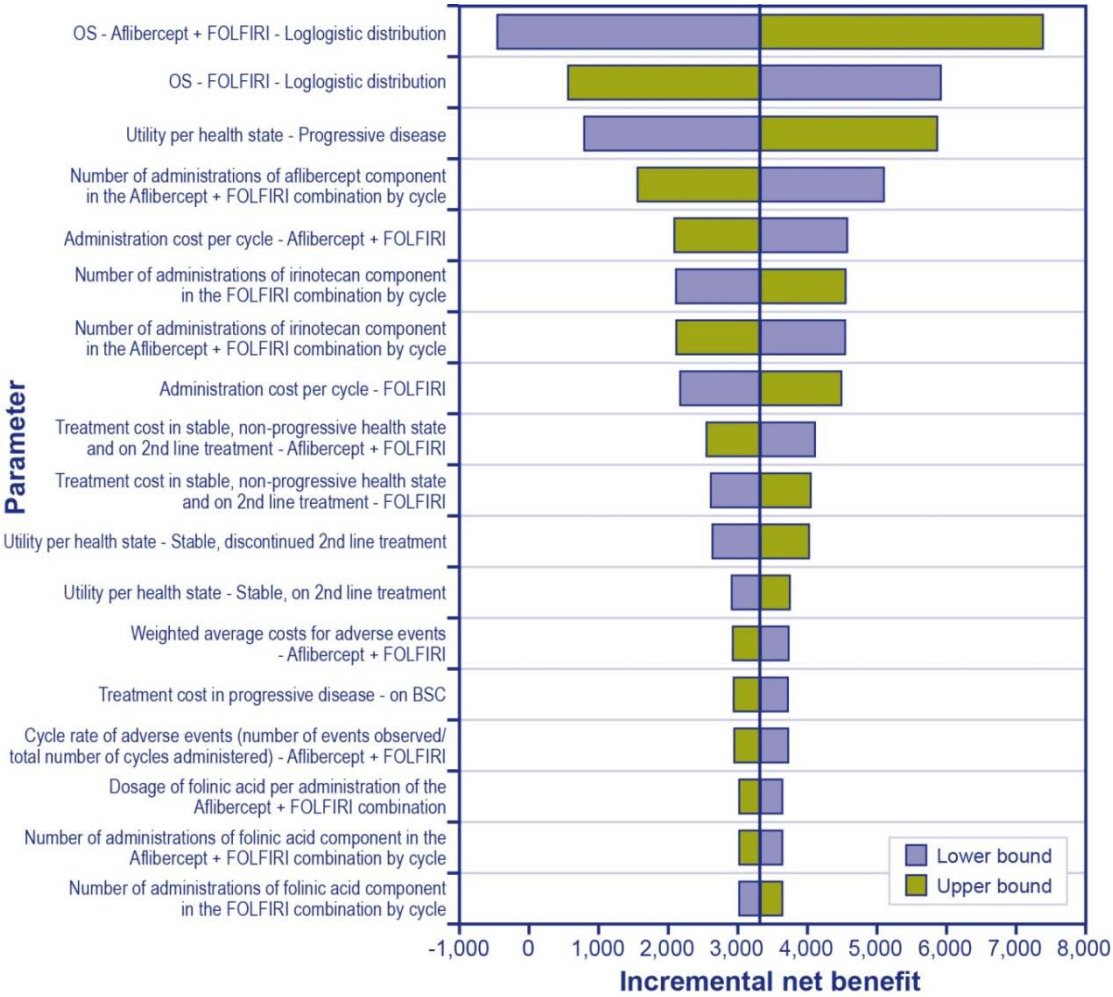
[b] Reference treatment for baseline incremental values.

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

In the deterministic sensitivity analysis, all model parameters were varied to 30% lower and 30% higher than the mean value. The results were expressed as the mean net monetary benefit and are presented as a tornado diagram in Figure B-19.

Figure B-21. **Univariate deterministic sensitivity analysis results**

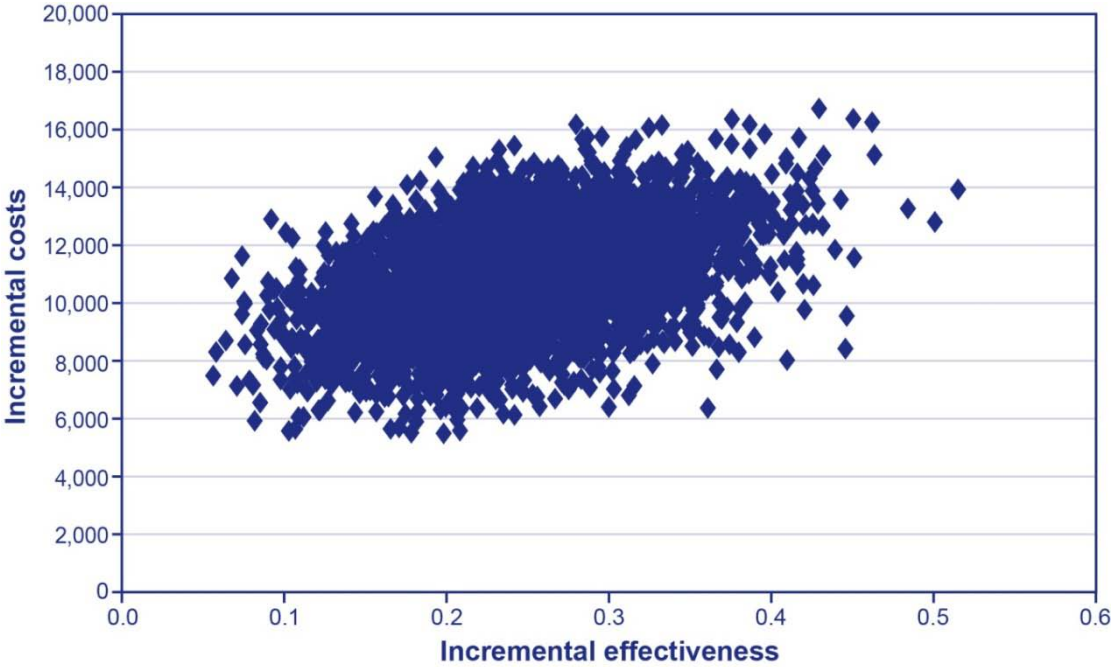


5-FU, 5-fluorouracil; FOLFIRI, 5 fluorouracil/leucovorin/irinotecan.

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

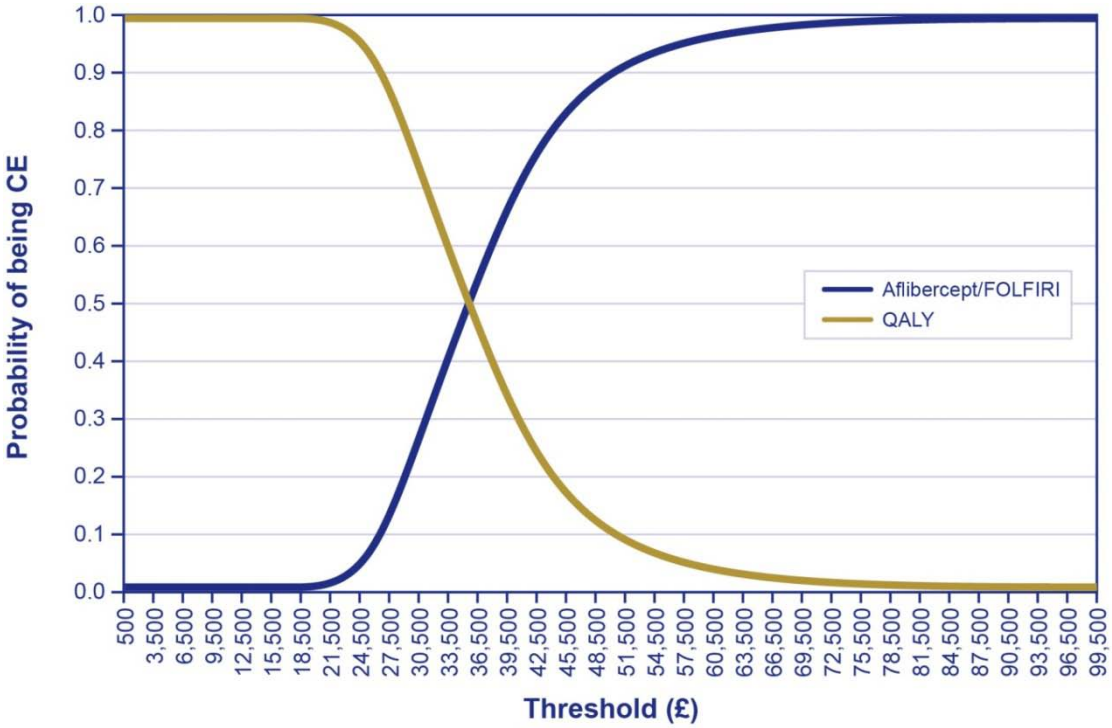
The results of the PSA are presented in Figure B-20 and Figure B-21.

Figure B-22. **PSA results presented on the cost-effectiveness plane**



PSA, progression-free survival.

Figure B-23. **Cost-effectiveness acceptability curves**



CE, cost-effectiveness; CEAC, cost-effectiveness acceptability curve.

7.7.9 *Please present the results of scenario analysis. Include details of structural sensitivity analysis.*

Structural uncertainty was investigated by applying alternative survival functions for PFS and OS and by directly applying Kaplan-Meier data for PFS. Alternative scenarios regarding drug wastage were explored, in which no drug was wasted (drug costs were calculated on a price-per-milligram basis) and in which patients requiring an amount of drug that was less than 5% higher than the amount contained in the nearest number of whole vials were "stepped down" to the nearest number of whole vials (the "5% step-down" scenario). The results are presented inTable B45.

Table B45. **Results of the scenario analyses**

Parameter	Base-case	Scenario	Incremental costs[a]	Incremental QALYs[a]	ICER
Base case results			8,816	0.2429	36,294
PFS function	Weibull	Log-logistic	8,562	0.2451	34,935
		Log-normal	8,594	0.2451	35,068
		Kaplan-Meier data	8,612	0.2429	35,459
		Weibull, progression determined by investigator assessment	8,802	0.2417	36,410
OS function	Log-logistic	Weibull	8,246	0.1656	49,805
		Log-normal	9,130	0.2702	33,788
Drug wastage	Unused drug in opened vials discarded[b]	No drug wastage (price per mg applied to mean dose)	[redacted]	[redacted]	[redacted]
		5% step-down scenario[a]	[redacted]	[redacted]	[redacted]
Management resource use from KOL survey	Median of KOL responses	Mean of KOL responses	10,013	0.2429	41,222
Time horizon	15 years	25 years	8,938	0.2587	34,549

5-FU, 5-fluorouracil; FOLFIRI, 5 fluorouracil/leucovorin/irinotecan; ICER, incremental cost-effectiveness ratio; KOL, key opinion leader, OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

[a] Aflibercept + FOLFIRI vs. FOLFIRI.

[b] The cost associated with wasted leucovorin and 5-FU was assumed to be negligible and similar for both treatments and was excluded from the analysis.

7.7.10 What were the main findings of each of the sensitivity analyses?

In the univariate sensitivity analysis, the ICER estimate was most sensitive the parametric assumptions regarding the distribution of overall survival, utility weight for the progressive

disease health state, and number of administrations of second-line treatment drugs. In the PSA, the probability of cost-effectiveness was 89.5% at a willingness-to-pay threshold of £50,000 per QALY. The probability was 22% at a WTP of £30,000 and 68% at a WTP of £40,000. In the scenario analyses, the ICER ranged from £32,729 to £49,805 per QALY.

7.7.11 What are the key drivers of the cost-effectiveness results?

The cost-effectiveness results suggest that aflibercept + FOLFIRI improves life-years and QALYs compared with FOLFIRI alone. These improvements in health outcomes were associated with an increase in total costs. Improvements in health outcomes were driven by an increase in overall survival and progression-free survival, as observed in the VELOUR trial. The increased costs estimated for aflibercept + FOLFIRI were due to greater drug costs, as well as an increase in post-progression costs as a result of the increase in survival.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Clinical validation of the model structure, parametric survival analyses, and parameter estimates was performed by an advisory board. Three advisory board meetings were held, one during the model-design phase and two after completion of the model..

Face validity was checked by a peer review board, a review committee consisting of internal senior scientists with extensive modelling and disease experience.

Quality control procedures included extreme-value sensitivity analyses and validation of the logical structure of the model, mathematical formulas and sequences of calculations, and the values of numbers supplied as model inputs. The model was reviewed by a peer reviewer not involved with the original programming.

Further validation was performed by an independent modelling group. All input data were verified with original sources; programming was checked to verify that formulae were applied correctly; range and logic checks were performed using extreme values; and key calculations were independently reproduced.

7.9 Subgroup analysis

7.9.1 *Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.*

Analysis was undertaken for two population subgroups:

- Patients with liver metastases only (pre-specified subgroup)
- ITT population excluding patients who had received oxaliplatin as adjuvant-tbased therapy and relapsed within 6 months of this

The rationale for exploring these subgroups is described in section 6.3.7

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Both subgroups are based on clearly defined characteristics. The liver metastases only subgroup consists of patients who only have metastases in the liver. The second subgroup excludes the patients from the trial who had relapsed within 6 months of adjuvant treatment. The baseline characteristics of patients in each subgroup by treatment arm are presented in in Appendix 15.

7.9.3 Please describe how the statistical analysis was undertaken.

Parametric survival functions were fitted to subgroup-specific data in the same way as described for the ITT population in sections 6.5.3 and 7.3.1. Details of the analyses are presented in appendix 15).

Liver metastases only subgroup

For OS, the log-logistic functions fitted separately to each treatment group were applied in the base-case analysis; other parametric functions were explored in sensitivity analysis.

For PFS, none of the functions appeared to provide an acceptable fit to the data. Because all patients had progressed during trial follow-up, the Kaplan-Meier data were applied in the base-case analysis. The parametric functions were investigated in sensitivity analysis.

Other data that were specific to the liver metastases only subgroup, such as duration of second-line treatment, number of administrations per cycle, dose intensity per administration, weight and BSA distributions, and AE probabilities (see section 7.3.6), are presented in Appendix 15.

No prior adjuvant therapy subgroup

For OS, the log-logistic functions fitted separately to each treatment group were applied in the base-case analysis; other parametric functions were explored in sensitivity analysis.

For PFS, none of the functions appeared to provide an acceptable fit to the data. Because all patients had progressed during trial follow-up, the Kaplan-Meier data were applied in the base-case analysis. The parametric functions were investigated in sensitivity analysis.

Other data that were specific to the ITT excluding adjuvant subgroup included the duration of second-line treatment, number of administrations per cycle, dose intensity per administration, weight and BSA distributions, and AE probabilities (see Section 7.3.6); these are presented in section Appendix 15.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

The results of the subgroup analyses are presented in Table B46.

Table B46. **Base-case results for the subgroup analyses**

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs. baseline (QALYs)	ICER (£) incremental (QALYs)
Isolated liver metastases								
FOLFIRI	[redacted]	[redacted]	[redacted]				—	—
Aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]	10,974	0.4955	0.3601	30,474	30,474
ITT excluding patients relapsing on or within 6 months of oxaliplatin-based adjuvant therapy								
FOLFIRI	[redacted]	[redacted]	[redacted]				—	—
Aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]	8,573	0.3668	0.2639	32,480	32,480

5-FU, 5-fluorouracil; FOLFIRI, 5 fluorouracil/leucovorin/irinotecan; ICER, incremental cost-effectiveness ratio; IRC, independent review committee; LYG, life-year gained; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

The results of the deterministic one-way sensitivity analyses, PSAs, and scenario analyses for the subgroups are presented in appendix 16. The probability of cost-effectiveness at a willingness-to-pay threshold of £50,000 per QALY was 93.04% for the liver metastases only group and 95.32% for the ITT excluding adjuvant therapy group.

7.9.5 *Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.*

There were no obvious subgroups that were not considered. Of the pre-specified subgroups, the only-liver metastases group showed a difference from the overall population and was therefore explored further. The only post hoc subgroup explored was that excluding patients relapsing rapidly after adjuvant therapy, which was accepted by the CHMP, as the group of excluded patients may represent a patient group with particularly aggressive disease. No subgroups identified in the decision problem were not considered.

7.10 ***Interpretation of economic evidence***

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

No published economic evaluations of aflibercept were identified.

7.10.2 *Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?*

The base-case in the economic evaluation is the licensed indication and therefore includes all groups of patients who could potentially use the technology according to the decision problem. As discussed previously, the patient populations included in the VELOUR trial, the resource use study, and the utility study, which form the primary data sources in the model, are all considered representative of the likely UK patient population (7.3.8 (Table B25). No issues were identified that would indicate that groups of patients who could potentially use the technology are not represented in the economic evaluation.

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

The main strengths of the analysis are as follows:

- The analysis is based on a head-to-head RCT that directly compared aflibercept + FOLFIRI with FOLFIRI; no indirect comparison was required. The VELOUR trial demonstrated statistically significant benefits for aflibercept + FOLFIRI.
- The PFS and OS data from the VELOUR trial are relatively mature and limited extrapolation is required.

- Structural uncertainty arising from alternative possible parametric survival functions, has been fully explored in sensitivity analysis.
- The duration of treatment, as well as dose delays and dose reductions, were captured in the VELOUR trial, and almost all patients had discontinued treatment during the trial follow-up period. Therefore, estimation of drug costs could be performed to a high degree of certainty and could be adjusted for the subgroup analyses.
- Resource use data for hospital care were based on a recent observational study of [redacted] patients performed in four centres in the UK (UK mCRC resource study).
- Utility data came from a recent observational study directly capturing EQ-5D data for [redacted] in routine clinical practice in the UK and the Netherlands (mCRC utilities study).
- The model design has been validated by a board of economic and clinical advisors, and independent validation of the model parameters and programming has been performed.

The main weaknesses of the economic evaluation are as follows:

- Given the paucity of published utility data, it is difficult to explore the impact of alternative utility sources on the ICER.
- As in many cancer models, assumptions made regarding costs post-progression may have a substantial impact where the appraised intervention increases the time spent in the post-progression health state. There is no clear empirical evidence from which it may be determined whether improving survival after disease progression results in increased overall per-patient costs post-progression, decreased costs, or similar costs. This uncertainty is inherent in this economic evaluation, as in many cancer models.

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

The ASQoP study is expected to provide high-quality utility estimates. Analyses applying these estimates would be of value.

No further analyses which would enhance the robustness or completeness of the results were identified.

Section C – Implementation

8 *Assessment of factors relevant to the NHS and other parties*

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

An estimated 4,028 patients will receive second-line treatment for mCRC in England and Wales in 2013 (ONS, 2011; ONS Welsh Cancer Intelligence and Surveillance Unit, 2011). Based on the proportion of patients with mCRC within the VELOUR trial population that had liver metastases only (Van Cutsem et al., 2012), an estimated 967 patients with mCRC and liver metastases will receive second-line treatment for mCRC in England and Wales in 2013. Based on the proportion of patients with mCRC within the VELOUR trial population that did not receive adjuvant treatment only (Van Cutsem et al., 2012), an estimated 3,625 patients will receive second-line treatment for mCRC in England and Wales in 2013.

Market-share data estimates that approximately 64% of patients receive oxaliplatin first-line and would therefore be eligible for aflibercept as per the licensed indication (Kantar Health 2011). This is applied to the numbers of pts receiving second-line treatment (above) to give an estimate of the number of second-line population who received prior oxaliplatin-based therapy and would therefore be eligible for aflibercept treatment in line with the license. This is likely to overestimate the number of patients eligible for FOLFIRI/ aflibercept, as some patients in the second-line setting who received prior oxaliplatin may not receive FOLFIRI (e.g. may receive less aggressive options such as capecitabine).

The estimated number of patients in each of these populations receiving treatment is projected for the years 2013 to 2017 (Table C-1). Estimates are presented using the assumption that there is no increase in the overall proportion of patients receiving treatment, as supported by age-standardised incidence data of bowel cancer from Cancer Research UK (2011), which has showed no meaningful change over the last 10 years.

Table C-1. Projected number of patients receiving second-line treatment for mCRC in England and Wales (2013-2017)

Patients	2013	2014	2015	2016	2017
All mCRC patients	2,578	2,578	2,578	2,578	2,578
mCRC patients with liver metastases only	619	619	619	619	619
mCRC patients excluding those receiving adjuvant treatment only	2,320	2,320	2,320	2,320	2,320

mCRC, metastatic colorectal cancer.

Sources: ONS 2011; ONS Welsh Cancer Intelligence and Surveillance Unit, 2011.

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

Currently, the second-line treatment option for patients with mCRC within England and Wales who would be eligible for aflibercept is FOLFIRI.

8.2 What assumption(s) were made about market share (when relevant)?

Projected market forecast estimates for aflibercept + FOLFIRI and FOLFIRI alone in 2013-2017, within the group of eligible patients, are presented in Table C-2. These estimates are the same for all mCRC patients, mCRC patients with liver metastases only, and mCRC patients not receiving adjuvant treatment.

Table C-2. Projected trend in market share for mCRC second-line treatments in England and Wales for 2013-1017

Treatment	Trend in market share (% treated patients)				
	2013	2014	2015	2016	2017
Aflibercept + FOLFIRI	15.00	25.00	40.00	50.00	58.85
FOLFIRI	85.00	75.00	60.00	50.00	41.15
Total market share	100.00	100.00	100.00	100.00	100.00

Source: Sanofi data on file, 2013.

The estimated numbers of patients receiving aflibercept + FOLFIRI also are presented in Table C-3. Estimated are presented for all mCRC patients, mCRC patients with liver metastases only, and mCRC patients excluding those receiving adjuvant treatment only.

Table C-3. Market forecast estimates for aflibercept + FOLFIRI in England and Wales: 2013-2017

Patients receiving aflibercept + FOLFIRI	2013	2014	2015	2016	2017
All patients with mCRC					
% patients	15.00	25.00	40.00	50.00	58.85
Number of patients	387	645	1,031	1,289	1,517
mCRC patients with liver metastases only					
% patients	15.00	25.00	40.00	50.00	58.85
Number of patients	93	155	248	310	364
mCRC patients excluding those receiving adjuvant treatment only					
% patients	15.00	25.00	40.00	50.00	58.85
Number of patients	348	580	928	1,160	1,365

FOLFIRI, 5 fluorouracil/leucovorin/irinotecan.

Source: Sanofi data on file 2013.

8.3 *In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).*

The annual costs associated with each treatment, including drug and administration costs, are presented in Table C-4. No other significant costs that may be of interest to commissioners were identified.

These costs are presented based on the aflibercept list price, i.e. not including the PAS. These costs and total costs below will be reduced in practice if the PAS is applied.

Table C-4. **Annual costs for mCRC second-line treatments (£, 2013)**

Treatment	Total (drug and administration)
Aflibercept + FOLFIRI	[redacted]
FOLFIRI	[redacted]

FOLFIRI, 5 fluorouracil/leucovorin/irinotecan; FOLFOX, folinic acid/5-fluorouracil/oxaliplatin; mCRC, metastatic colorectal cancer.

Sources: Van Cutsem et al., 2012; Kantar Health, 2011; BNF, 2012; NHS Reference Costs, 2011; Clarke et al., 2011; Sanofi data on file, 2013.

8.4 *What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?*

Unit costs and cost calculations are summarised below.

[redacted] All calculations for drug costs used these assumptions to determine the amount of drug used.

Table C-5 presents the treatment duration for each of the drugs considered, and Table C-6 presents the acquisition costs for each of the drugs considered.

Administration costs also were considered. All treatment regimens are provided in hospital by IV infusion, at a cost of £331.36 each administration, whether first or subsequent (NHS Reference Costs, 2012).

Table C-5. **Treatment duration for each drug**

Treatment	Chemotherapy (# cycle)	Chemotherapy (# weeks/cycle)	Add-on drug (# cycle)	Add-on drug (# weeks/cycle)
Aflibercept + FOLFIRI	[redacted]	2	[redacted]	2
FOLFIRI	[redacted]	2		

FOLFIRI, 5 fluorouracil/leucovorin/irinotecan; FOLFOX, folinic acid/5-fluorouracil/oxaliplatin.

Sources: Van Cutsem et al., 2012; Kantar Health, 2011; Clarke et al., 2011.

Table C-6. Acquisition costs for drugs of interest

Costs by drug	Dosing regimen	Vial size (mg)	Vial cost (£)	Per loading dose (£)	Per maintenance dose (£)
FOLFIRI: irinotecan	180 mg/m^2 IV over 90 minutes, every 2 weeks	100	120.25	—	481
FOLFIRI: folinic acid (leucovorin)	400 mg/m^2 IV over 2 hours, every 2 weeks	100	35.09	—	280.72
FOLFIRI: fluorouracil (5-FU)	400 mg/m^2 IV bolus over 2-4 minutes, then 2400 mg/m^2 continuous IV infusion over 46 hours, every 2 weeks	250	3.2	—	67.20
Aflibercept	4 mg/kg IV over 1 hour, every 2 weeks	100	295.65 (list price)	—	
		200	591.30 (list price)		

FOLFIRI, 5 fluorouracil/leucovorin/irinotecan; FOLFOX, folinic acid/5-fluorouracil/oxaliplatin; IV, intravenous.

Sources: Van Cutsem et al., 2012; Kantar Health, 2011; BNF, 2012; Sanofi data on file, 2013.

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

There were no estimates of resource savings considered.

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

Estimated costs to NHS budgets in England and Wales are presented in Table C-7 for scenarios in which aflibercept is recommended and is not recommended. The estimated budget impact of recommending aflibercept is presented in Table C-8. Estimates are presented for all mCRC patients, mCRC patients with liver metastases only, and mCRC patients not receiving adjuvant treatment.

Table C-7. Estimated costs in England and Wales for all mCRC patients, mCRC patients with liver metastases only, and mCRC patients excluding those receiving adjuvant treatment only

Scenario for each patient population	Cost (£)				
	2013	2014	2015	2016	2017
All mCRC patients					
Cost of aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of other interventions if aflibercept is not recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of other interventions if aflibercept is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs if aflibercept is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mCRC patients with liver metastases only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of other interventions if aflibercept is not recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of other interventions if aflibercept is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs if aflibercept is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mCRC patients excluding those not receiving adjuvant treatment only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of aflibercept + FOLFIRI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of other interventions if aflibercept is not recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of other interventions if aflibercept is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs if aflibercept is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FOLFIRI, 5 fluorouracil/leucovorin/irinotecan.

Source: Sanofi data on file, 2013.

Table C-8. **Estimated impact of recommending aflibercept on NHS budgets in England and Wales for all mCRC patients, mCRC patients with liver metastases only, and mCRC patients excluding those receiving adjuvant treatment only**

Patient population	Cost (£)				
	2013	2014	2015	2016	2017
All mCRC patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mCRC patients with liver metastases only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mCRC patients, excluding those receiving adjuvant only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

mCRC, metastatic colorectal cancer; NHS, National Health Service.

Source: Sanofi data on file, 2013.

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

No other opportunities for resource savings have been identified.

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