National Institute for Health and Care Excellence

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Colorectal cancer (update)

[C8] Optimal duration of adjuvant chemotherapy for colorectal cancer

NICE guideline NG151

Evidence reviews

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Developed by the National Guideline Alliance part of the Royal College of Obstetricians and Gynaecologists

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Optimal duration of adjuvant chemotherapy for colorectal cancer

This evidence review supports recommendation 1.3.14.

Review question

What is the optimal duration of adjuvant chemotherapy for colorectal cancer?

Introduction

Adjuvant chemotherapy for 24 weeks (6 months) has previously been established as the standard of care for stage III colorectal cancer (Andre 2003). In recent years a shorter duration of adjuvant chemotherapy have been suggested in order to minimise the adverse long-term effects of chemotherapy, mainly neurotoxicity. This review aims to find out what is the optimal duration of adjuvant chemotherapy for colorectal cancer taking into consideration its effects on for example survival and cancer recurrence, neurotoxicity and quality of life.

Summary of the protocol

Please see Table 1 for a summary of the population, intervention, comparison and outcomes (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults with non-metastatic colorectal cancer after receiving surgery with curative intent Subgroups to be considered separately: • pT4 • pT3/T4 N0 with vascular invasion • right versus left sided tumour • age over 70 years
Intervention	• Adjuvant chemotherapy for less than 24 weeks (6 months)
Comparison	• Adjuvant chemotherapy for 24 weeks (6 months)
Outcomes	**Critical** • Disease-free survival • Overall survival • Neuropathy (lasting for 2 years considered permanent) **Important** • Overall quality of life • Distant metastasis • Treatment-related mortality • Dose reduction

N: nodal stage; p: pathological staging; T: tumour stage

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

Seven RCTs (reported in 7 publications) were included. Data from 6 RCTs (TOSCA, SCOT, IDEA France, CALGB/SWOG, HORG, ACHIEVE) were reported in 1 collaborative paper (Grothey 2018) which pooled individual patient data from these studies. Additional data from 3 of these 6 RCTs were also reported in separate publications (IDEA France [Andre 2018]; SCOT [Iveson 2018]; TOSCA [Lonardi 2016]). One RCT (reported in 3 publications) was also included (Chau 2005a; Chau 2005b; Saini 2003).

The included studies are summarised in Table 2.

The collaborative paper (Grothey 2018), combined individual patient data from 6 RCTs (TOSCA, SCOT, IDEA France, CALGB/SWOG, HORG, ACHIEVE) to compare 3 months and 6 months of oxaliplatin-based adjuvant chemotherapy, either folinic acid plus fluorouracil plus oxaliplatin (FOLFOX) or oxaliplatin plus capecitabine (CAPOX), in people with colon cancer (IDEA Collaboration 2018; IDEA France [Andre 2018]; SCOT [Iveson 2018]; TOSCA [Lonardi 2016]). An RCT within the IDEA Collaboration also included people with rectal cancer (SCOT).

One RCT compared 3 months of protracted fluorouracil infusion to 6 months of bolus fluorouracil plus folinic acid (leucovorin) (Chau 2005; Chau 2005a; Chau 2005b; Saini 2003).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included clinical studies

Study	Population	Intervention/Comparison	Outcomes
Comparison 1: 3 months versus 6 months of oxaliplatin-based adjuvant chemotherapy			

Study	Population	Intervention/Comparison	Outcomes
IDEA collaboration (Grothey 2018) Individual patient data from 6 RCTs: • TOSCA (Italy) • SCOT (UK, Denmark, Spain, Australia, Sweden, New Zealand) • IDEA France • CALGB/SWOG (US, Canada) • HORG (Greece) • ACHIEVE (Japan)	N=12,834 people with stage III colon cancer • TOSCA n=2,402 • SCOT n=3,983 • IDEA France n=2,010 • CALGB/SWOG n=2,440 • HORG n=708 • ACHIEVE n=1,291	3 months versus 6 months of adjuvant chemotherapy Type of chemotherapy: • folinic acid, fluorouracil and oxaliplatin (FOLFOX), 60% • capecitabine and oxaliplatin (CAPOX), 40%	• Disease-free survival • Grade 3 or 4 peripheral neurotoxicity • Percentage of chemotherapy dose delivered
IDEA France trial (Andre 2018) RCT France	N=2,022 people aged 18 years or older with stage III colon cancer	3 months versus 6 months of adjuvant chemotherapy Type of chemotherapy: • folinic acid, fluorouracil and oxaliplatin (FOLFOX), 90% • capecitabine and oxaliplatin (CAPOX), 10%	• Overall survival • Treatment-related mortality Disease-free survival, neurotoxicity and dose reduction from the IDEA France trial are reported within the pooled analysis of the IDEA collaboration trials in Grothey 2018.
SCOT trial (Iveson 2018) RCT UK, Denmark, Spain, Sweden, Australia, and New Zealand	N=6,088 people aged 18 years or older with stage III or high-risk stage II colon or rectal cancer	3 months versus 6 months of adjuvant chemotherapy Type of chemotherapy: • folinic acid, fluorouracil and oxaliplatin (FOLFOX), 33% • capecitabine and oxaliplatin (CAPOX), 67%	• Disease-free survival (for people with rectal cancer) • Overall survival • Quality of life • Treatment-related mortality Disease-free survival (for people with colon cancer), neurotoxicity, and dose reduction from the SCOT trial are reported within the pooled analysis of the IDEA collaboration trials in Grothey 2018.
TOSCA trial (Lonardi 2016) RCT	N=3,759 people aged 18 years or older with stage III or high-risk stage II colon cancer	3 months versus 6 months of adjuvant chemotherapy	• Treatment-related mortality

Study	Population	Intervention/Comparison	Outcomes
Italy		Type of chemotherapy: • folinic acid, fluorouracil and oxaliplatin (FOLFOX), 64% • capecitabine and oxaliplatin (CAPOX), 36%	Disease-free survival and neurotoxicity are reported within the pooled analysis of the IDEA collaboration trials in Grothey 2018.
Comparison 2: 3 months of fluorouracil infusion versus 6 months of bolus fluorouracil/leucovorin			
Chau 2005 (Chau 2005a; Chau 2005b; Saini 2003) RCT UK	N=826 people with curatively resected stage II and III adenocarcinoma of the colon or rectum	12 weeks of protracted venous infusion of fluorouracil versus 6 months of bolus fluorouracil/leucovorin	• Disease-free survival • Overall survival • Quality of life • Distant metastasis • Chemotherapy-related mortality • Percentage of chemotherapy dose delivered

N: number; RCT: randomised controlled trial

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of clinical studies included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

One relevant study was identified in a literature review of published cost-effectiveness analyses on this topic (Robles-Zurita 2018; see appendix H and appendix I for summary and full evidence tables). The study compared a 3 month to a 6 month regimen of adjuvant chemotherapy in patients with fully resected high-risk stage II or stage III colorectal cancer. The study compared the length of adjuvant chemotherapy separately for both CAPOX and FOLFOX.

The economic analysis was a within study cost-utility analysis with all resource use and outcome data collected alongside the SCOT RCT considered in the clinical evidence review (Iveson 2018). The study took a NHS & PSS perspective.

Excluded studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Clinical evidence statements

Comparison 1: 3 months versus 6 months of oxaliplatin-based adjuvant chemotherapy for colorectal cancer

Critical outcomes

Disease-free survival

- High quality evidence from meta-analysis of individual patient data from 6 RCTs (N=12,834; median follow-up 3.5 years) showed that there may be a clinically important lower disease-free survival in people who received 3 months adjuvant chemotherapy compared to 6 months of adjuvant chemotherapy for non-metastatic colon cancer, but there is uncertainty around the estimate.
- High quality evidence from meta-analysis of individual patient data from 6 RCTs (N=5,071; median follow-up 3.5 years) showed no clinically important difference in disease-free survival in the subpopulation of people who received 3 months or 6 months of adjuvant CAPOX chemotherapy for non-metastatic colon cancer.
- High quality evidence from meta-analysis of individual patient data from 6 RCTs (N=7,763; median follow-up 3.5 years) showed a clinically important lower disease-free survival for subpopulation of people who received 3 months of adjuvant FOLFOX chemotherapy compared to 6 months of adjuvant FOLFOX chemotherapy for non-metastatic colon cancer.
- High quality evidence from meta-analysis of individual patient data from 6 RCTs (N=2,655; median follow-up 3.5 years) showed a clinically important lower disease-free survival for subpopulation of people with stage T4 colon cancer who received 3 months of adjuvant chemotherapy compared to 6 months of adjuvant chemotherapy.
- High quality evidence from meta-analysis of individual patient data from 6 RCTs (N=7,471; median follow-up 3.5 years) showed no clinically important difference in disease-free survival in the subpopulation of people with stage T1-3N1 colon cancer who received 3 months or 6 months of adjuvant chemotherapy.
- High quality evidence from meta-analysis of individual patient data from 6 RCTs (N not reported; median follow-up 3.5 years) showed that there may be a clinically important better disease-free survival in the subpopulation of people with stage T1-3N1 colon cancer who received 3 months of adjuvant CAPOX chemotherapy compared to 6 months of adjuvant CAPOX chemotherapy, but there is uncertainty around the estimate.
- High quality evidence from meta-analysis of individual patient data from 6 RCTs (N not reported; median follow-up 3.5 years) showed no clinically important difference in disease-free survival in the subpopulation of people with stage T1-3N1 colon cancer who received 3 months or 6 months of adjuvant FOLFOX chemotherapy.
- High quality evidence from meta-analysis of individual patient data from 6 RCTs (N=5,256; median follow-up 3.5 years) showed a clinically important lower disease-free survival for the subpopulation of people with stage T4 and/or N2 colon cancer who received 3 months of adjuvant chemotherapy compared to 6 months of adjuvant chemotherapy.
- High quality evidence from meta-analysis of individual patient data from 6 RCTs (N not reported; median follow-up 3.5 years) showed no clinically important difference in disease-free survival in the subpopulation of people with stage T4 and/or

N2 colon cancer who received 3 months or 6 months of adjuvant CAPOX chemotherapy.

- High quality evidence from meta-analysis of individual patient data from 6 RCTs (N not reported; median follow-up 3.5 years) showed a clinically important lower disease-free survival for the subpopulation of people with stage T4 and/or N2 colon cancer who received 3 months of adjuvant FOLFOX chemotherapy compared to 6 months of adjuvant FOLFOX chemotherapy.
- Moderate quality evidence from 1 RCT (N=1,098; median follow-up 3.1 years) showed no clinically important difference in disease-free survival in the subpopulation of people with non-metastatic rectal cancer who received 3 months or 6 months of adjuvant chemotherapy.

Overall survival

- High quality evidence from 2 RCTs (N=8,075; median follow-up 3.1 to 4.3 years) showed no clinically important difference in overall survival between 3 months and 6 months of adjuvant chemotherapy for people with non-metastatic colorectal cancer.
- Moderate quality evidence from 1 RCT (N=201; median follow-up 4.3 years) showed no clinically important difference in overall survival in the subpopulation of people who received 3 months or 6 months of adjuvant CAPOX chemotherapy for non-metastatic colon cancer.
- Moderate quality evidence from 1 RCT (N=1,809; median follow-up 4.3 years) showed no clinically important difference in overall survival in the subpopulation of people who received 3 months or 6 months of adjuvant FOLFOX chemotherapy for non-metastatic colon cancer.

Neuropathy

- Moderate quality evidence from meta-analysis of individual patient data from 6 RCTs (N=12,834) showed a clinically important lower risk of grade 3 or 4 neuropathy in people who received 3 months of adjuvant chemotherapy compared to 6 months of adjuvant chemotherapy for non-metastatic colon cancer.
- Moderate quality evidence from meta-analysis of individual patient data from 6 RCTs (N=12,834) showed a clinically important lower risk of grade 3 or 4 neuropathy in the subpopulation of people who received 3 months of adjuvant CAPOX chemotherapy compared to 6 months of adjuvant chemotherapy for non-metastatic colon cancer.
- Moderate quality evidence from meta-analysis of individual patient data from 6 RCTs (N=12,834) showed a clinically important lower risk of grade 3 or 4 neuropathy in the subpopulation of people who received 3 months of adjuvant FOLFOX chemotherapy compared to 6 months of adjuvant chemotherapy for non-metastatic colon cancer.

Important outcomes

Overall quality of life

- Moderate quality evidence from 1 RCT (N=6,088) showed a clinically important better quality of life (measured using QLQ-C30 global health status score and EQ-5D VAS) at 6 months in people who received 3 months of adjuvant chemotherapy compared to 6 months of adjuvant chemotherapy for non-metastatic colorectal cancer. There was no difference in quality of life at 12 months (measured using the same scales).

Distant metastasis

No evidence was identified to inform this outcome.

Treatment-related mortality

- Moderate quality evidence from 3 RCTs (N=11,729) showed no clinically important difference in treatment-related mortality between 3 months and 6 months of adjuvant FOLFOX chemotherapy for people with non-metastatic colorectal cancer.

Dose reduction

- High quality evidence from meta-analysis of individual patient data from 6 RCTs (N=5,071) showed a clinically important higher percentage of planned oxaliplatin dose delivered in the subpopulation of people who received 3 months of adjuvant CAPOX chemotherapy compared to 6 months of adjuvant CAPOX chemotherapy for non-metastatic colon cancer.
- High quality evidence from meta-analysis of individual patient data from 6 RCTs (N=7,763) showed a clinically important higher percentage of planned oxaliplatin dose delivered in the subpopulation of people who received 3 months of adjuvant FOLFOX chemotherapy compared to 6 months of adjuvant FOLFOX chemotherapy for non-metastatic colon cancer.
- High quality evidence from meta-analysis of individual patient data from 6 RCTs (N=7,763) showed a clinically important higher percentage of planned fluorouracil dose delivered in the subpopulation of people who received 3 months of adjuvant FOLFOX chemotherapy compared to 6 months of adjuvant FOLFOX chemotherapy for non-metastatic colon cancer.
- High quality evidence from meta-analysis of individual patient data from 6 RCTs (N=5,071) showed a clinically important higher percentage of planned capecitabine dose delivered in the subpopulation of people who received 3 months of adjuvant CAPOX chemotherapy compared to 6 months of adjuvant CAPOX chemotherapy for non-metastatic colon cancer.

Comparison 2: 3 months of fluorouracil infusion versus 6 months of bolus fluorouracil/leucovorin

Critical outcomes

Disease-free survival

- Moderate quality evidence from 1 RCT (N=801; median follow-up 5.4 years) showed that there may be a clinically important better disease-free survival in people who received 3 months of fluorouracil infusion compared to 6 months of bolus fluorouracil and leucovorin for non-metastatic colorectal cancer, but there is uncertainty around the estimate.
- Moderate quality evidence from 1 RCT (N=323; median follow-up 4.6 years) showed a clinically important better survival in the subpopulation of people with non-metastatic rectal cancer who received 3 months of fluorouracil infusion compared to 6 months of bolus fluorouracil and leucovorin.

Overall survival

- Moderate quality evidence from 1 RCT (N=801; median follow-up 5.4 years) showed that there may be a clinically important better overall survival in people who received 3 months of fluorouracil infusion compared to 6 months of bolus

fluorouracil and leucovorin for non-metastatic colorectal cancer, but there is uncertainty around the estimate.

- Moderate quality evidence from 1 RCT (N=323; median follow-up 4.6 years) showed that there may be a clinically important better overall survival in the subpopulation of people with non-metastatic rectal cancer who received 3 months of fluorouracil infusion compared to 6 months of bolus fluorouracil and leucovorin for non-metastatic colorectal cancer, but there is uncertainty around the estimate.

Neuropathy

No evidence was identified to inform this outcome.

Important outcomes

Overall quality of life

- Very low quality evidence from 1 RCT (N=801) showed no clinically important difference in quality of life at 24 weeks and at 2 years after randomisation (measured using QLQ-C30 global health status score) in people who received 3 months of fluorouracil infusion compared to 6 months of bolus fluorouracil and leucovorin for non-metastatic colorectal cancer.

Distant metastasis

- Moderate quality evidence from 1 RCT (N=801) showed no clinically important difference in distant metastasis in people who received 3 months of fluorouracil infusion or 6 months of bolus fluorouracil and leucovorin for non-metastatic colorectal cancer.

Treatment-related mortality

- High quality evidence from 1 RCT (N=801) showed that there were no chemotherapy-related deaths in people with non-metastatic colorectal cancer in either the 3-month or 6-month chemotherapy arms.

Dose reduction

- High quality evidence from 1 RCT (N=692) showed a clinically important higher percentage of dose delivered in people who received 3 months of fluorouracil infusion compared to 6 months of bolus fluorouracil and leucovorin for non-metastatic colorectal cancer.

Economic evidence statements

One cost utility analysis showed that for people receiving CAPOX chemotherapy a 3 month course is both cost saving and more effective compared to a 6 month course with a less than 1% probability that the 6-month regimen provides a cost effective use of NHS resources when QALYs are valued at £20,000 each. The same analysis showed that whilst a 3 month course of FOLFOX chemotherapy would be less effective it would also be cost saving. The saving per QALY forgone was greater than £50,000 suggesting that the 3 month course would be cost effective if QALYs are valued at £20,000 each. There was a less than 10% probability of a 6 month course being cost effective when QALYs are valued at £20,000 each. The study took an NHS perspective and was considered directly applicable to the decision problem with only minor methodological limitations.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to compare the effectiveness and safety of a shorter duration of adjuvant chemotherapy to the standard 6 months of adjuvant chemotherapy for people with colorectal cancer. Disease-free survival and overall survival were considered critical outcomes for decision-making because ultimately the aim of cancer treatment is to improve survival. Neuropathy was also considered a critical outcome as it is the main long-term adverse effect of chemotherapy which can have a significant negative impact on people's lives.

Quality of life was considered an important outcome as it can capture many aspects of the benefits and harms of treatment. Distant metastasis was also considered an important outcome as it often related to survival and the need for further treatment. Dose reduction was considered an important outcome as it reflects the short-term toxicity of the treatment as well as its effectiveness.

The quality of the evidence

Evidence was available for the comparison of 3 months versus 6 months of oxaliplatin-based adjuvant chemotherapy for colorectal cancer (comparison 1), and for the comparison of 3 months of fluorouracil infusion versus 6 months of bolus fluorouracil/leucovorin (comparison 2).

For comparison 1, evidence was available for all of the outcomes except distant metastasis and for comparison 2, evidence was available for all of the outcomes except neuropathy. The quality of the evidence was assessed using GRADE and was mostly of high quality, varying from low to high.

The main reasons for downgrading the quality of the evidence were imprecision of the effect estimate, and lack of blinding for outcomes that were considered to be subjective (quality of life and neuropathy were both measured using patient self-reported questionnaires).

Benefits and harms

Six months of adjuvant oxaliplatin-based chemotherapy has been the standard of care after surgery for stage III colorectal cancer patients (apart from rectal cancer patients who have received long-course chemoradiotherapy preoperatively). However, the major long-term adverse effect of oxaliplatin-based chemotherapy is peripheral neuropathy that can have significant effects on a person's quality of life. The committee agreed that it is important to find a balance where the long-term toxicity of chemotherapy could be minimised without compromising its beneficial effect on survival and disease recurrence. In addition, the committee discussed that it is important to consider patient characteristics, including age, performance status, and comorbidities as well as the histopathology of the cancer when considering difference options of treatment, particularly in relation to the side-effects of the different treatment options.

The evidence showed that the rate of severe neuropathy was considerably lower with 3 months of chemotherapy compared to the standard 6 months of chemotherapy (1.8% versus 10% of the patients having grade 3 or 4 peripheral neuropathy). There was no difference in chemotherapy-related mortality. The percentage of total planned dose of chemotherapy received was higher among people in the 3-month group

(around 90% for oxaliplatin) than those in the 6-month group (around 70% for oxaliplatin). This finding suggests that 3 months of chemotherapy was better tolerated and there was less need for dose reductions due to side-effects.

In terms of disease-free survival the findings were more complex. In the total population, regardless of disease stage or chemotherapy regimen, the evidence suggested that disease-free survival might be worse in the 3-month group (74.6% [95% CI 73.5% to 75.7%] at 3 years) than in the 6-month group (75.5% at 3 years), although there is uncertainty around the estimate and the differences are small. However, when stratifying according to the treatment regimen (CAPOX or FOLFOX), the findings showed that 3 months of CAPOX chemotherapy was as effective as 6 months of CAPOX (75.9% [95% CI 74.2% to 77.6%] versus 74.8% at 3 years) whereas FOLFOX chemotherapy for 3 months showed worse disease-free survival than FOLFOX for 6 months (73.6% [95% CI 72.2% to 75.1%] versus 76.0% at 3 years). Stratifying further according to cancer stage, the evidence suggested that for people who received CAPOX and had “low risk” cancer (stage T1-3 and N1), 3 months of CAPOX may actually be better than 6 months of CAPOX in terms of disease-free survival (85.0% [95% CI 83.1% to 86.9%] versus 83.1% at 3 years). For people who received FOLFOX and had “low risk” cancer there was no statistically significant difference between the groups (81.9% [95% CI 80.2% to 83.6%] versus 83.5% at 3 years). For people with “high risk” cancer (stage T4 and/or N2) who received CAPOX, there was no difference in disease-free survival between the groups suggesting that 3 months is as effective as 6 months of CAPOX chemotherapy (64.1% [95% CI 61.3% to 67.1%] versus 64.0% at 3 years). On the other hand, those with “high risk” cancer who received FOLFOX, 3 months of FOLFOX showed worse disease-free survival than 6 months of FOLFOX (61.5% [95% CI 58.9% to 64.1%] versus 64.7% at 3 years).

Evidence on overall survival showed no difference between the different durations although evidence for the total population was only available from 2 of the IDEA collaboration trials and from only 1 trial stratified by treatment regimen and thus lacks statistical power.

The committee were aware that the trials making up the IDEA collaboration were designed to compare 3 months with 6 months of chemotherapy but were not designed to compare the duration according to the chemotherapy regimen (FOLFOX and CAPOX) or by cancer stage. The analyses of regimen and cancer stage were thus exploratory in nature. The large size of the IDEA collaboration however provides high quality evidence. In addition, it should be noted that the IDEA collaboration based their interpretation of the results to a non-inferiority level of 1.12 (meaning that non-inferiority of 3 months was proven only if the upper confidence interval of the hazard ratio did not exceed 1.12, which corresponds to about 2.7 percentage point difference in disease-free survival). As outlined in the review protocol, the committee on the other hand considered statistical significance as the basis for judging if there is a clinically important difference.

Weighing the benefits and harms of the different chemotherapy durations and regimens, the committee agreed that people with colon cancer should be offered CAPOX chemotherapy for 3 months as it has lower long-term toxicity but equal effect on disease relapse and survival. Non-inferiority was seen for the entire treatment group and in the exploratory analysis of “low risk” patients. In the “high risk” patient population no difference in 3-year disease free survival was observed even though the IDEA collaboration concluded that statistical non-inferiority was not confirmed due to the upper confidence interval of the hazard ratio exceeding 1.12. Regardless, the committee agreed that the risk of peripheral neuropathy significantly outweighs any possible benefit of continuing CAPOX for 6 months in the “high risk” group of patients. The

committee therefore recommended 3 months of CAPOX chemotherapy for all patients. Both capecitabine and oxaliplatin (drugs in the CAPOX regimen) are generic drugs and used widely in current practice in the UK.

However, the committee recognised that CAPOX is not appropriate for all people because of the side-effects of treatment. CAPOX is taken every 3 weeks with a large dose of oxaliplatin and may cause side-effects such as fatigue, nausea, and diarrhoea that people with comorbidities or who are frail might have difficulty tolerating. Analysis from the SCOT trial showed higher rates of severe diarrhoea and hand foot syndrome with CAPOX chemotherapy. Therefore, the committee agreed that FOLFOX chemotherapy should be discussed as an alternative for such people. The optimal duration of FOLFOX chemotherapy was difficult to determine as 6-month course showed better disease-free survival but 3-month course showed less long-term toxicity (neuropathy) and considerably less costs. Another alternative to oxaliplatin containing chemotherapy which the committee recommended is single agent capecitabine chemotherapy for 6 months. Single agent treatment is known to be less effective than combination chemotherapy including capecitabine but is associated with lower incidence of severe side-effects. This treatment is particularly well tolerated in patients over 70 years of age who appear to gain little benefit from the addition of oxaliplatin. Single agent capecitabine has been recommended by previous NICE technology appraisal on capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer (TA100).

Not surprisingly, the 3-month group had a better overall quality of life at 6 months, when the 6-month group is still on or about to finish chemotherapy. However, the committee was surprised that no difference was observed in the quality of life at 1 year between the groups even though severe neuropathy was much more common in the 6-month group.

People who received preoperative long-course radiotherapy or chemoradiotherapy were not eligible for the IDEA collaboration trials. Therefore, rectal cancer patients who had received preoperative long-course chemoradiotherapy are not covered by these recommendations. Despite the lack of evidence among these people, a research recommendation was not made because trials of adjuvant chemotherapy after long-course radiotherapy or chemoradiotherapy have previously been attempted but closed early due to poor recruitment (Glynne-Jones 2014). The focus of national and international treatment has moved to intensifying pre-operative treatment with studies investigating intensified chemo-radiotherapy regimens and sequences of pre-operative systemic chemotherapy and pelvic radiotherapy (ARITOTLE trial, www.isrctn.com/ISRCTN09351447, accessed 6 June 2019).

The SCOT trial, the largest trial within the IDEA collaboration, however, included rectal cancer patients if they had had either short-course radiotherapy or no preoperative therapy. Stratified analysis among these rectal cancer patients showed that the main outcomes were similar for them as for the colon cancer patients, therefore, the committee agreed that the recommendations for colon cancer patients apply equally to those rectal cancer patients who have not received preoperative long-course chemoradiotherapy.

The committee was also interested in the influence of age on the effectiveness of the different chemotherapy durations. They were aware that previous studies comparing fluorouracil therapy with or without oxaliplatin have shown reduced or no benefit of oxaliplatin in patients over 70 years of age (McCleary 2013) and because of these findings, many patients aged 70 years or older are considered for single agent treatment alone (without oxaliplatin) in current practice. The available studies did not pro-

vide results according to age and even if they would have the IDEA collaboration trials included oxaliplatin in both intervention arms so the effect on age shown in the previous studies was not applicable. Because there is no age-stratified evidence on the effect of duration of chemotherapy, the committee was not able to make recommendations according to the age of the patient.

The review also included an earlier UK trial comparing 3 months of protracted fluorouracil infusion to 6 months of bolus fluorouracil and folinic acid (leucovorin). The findings showed that 3-month chemotherapy may be better in terms of disease-free survival and overall survival. However, the committee discussed that this trial did not change practice when it was published because it was relatively small and underpowered. In current UK practice, oral capecitabine is given as the treatment of choice. Neither the bolus or infusional fluorouracil regimens investigated in the trial are used routinely and therefore the interventions were not considered to be relevant for current practice and the findings from this trial did not inform the recommendations made.

Cost effectiveness and resource use

The literature search of previous economic evidence identified 1 economic evaluation relevant to this topic. The study (Robles-Zurita 2018) compared a 3 month to a 6 month regimen of adjuvant chemotherapy in patients with fully resected high-risk stage II or stage III colorectal cancer. The study compared the length of adjuvant chemotherapy for 2 regimens-CAPOX and FOLFOX.

The study took a NHS & PSS perspective and was deemed to only have minor methodological issues. The economic analysis was a within study cost-utility analysis with all resource use and outcome data collected alongside the SCOT RCT considered in the clinical evidence review (Iveson 2018). The RCT was conducted across 2 Australasian and 4 European countries including the UK and the quality of all clinical outcomes were rated either moderate or high using GRADE criteria. Quality of life in the study was collected at baseline and all follow-up meetings in a subsection of 1,832 patients equating to about 30% of the entire trial population. The EQ-5D-3L questionnaire was used and scored using the UK general population tariffs, the preferred method of NICE. All resource use was costed using publically available UK costs.

The study found that a 3-month regimen of either CAPOX or FOLFOX led to cost savings of £3,853 and £6,481 respectively during a maximum follow-up of 8 years. CAPOX for 3 months led to an increase in both life expectancy (0.07 years) and QALYs (0.19) dominating the 6-month regimen. The increase in QALYs is most likely driven by reduced toxicity with a shorter duration of treatment and a reduction in significant peripheral neuropathy. In the FOLFOX group moving from a 6- to a 3-month regimen led to a reduction in both life expectancy (-0.22 years) and QALYs (-0.12) although neither were statistically significant. This led to a saving of over £50,000 for every QALY forgone. The 3-month FOLFOX regimen would be cost effective under the conventional NICE threshold of £20,000 per QALY. Both these results were robust during probabilistic sensitivity analysis with a >99% probability of 3-month CAPOX and >90% probability of 3-month FOLFOX being the preferred option at a threshold of £20,000 per QALY. No deterministic sensitivity analyses were presented.

The committee acknowledged that directly applicable, high quality economic evidence was identified for this topic area and noted that it strongly favoured the 3-month regimen for both CAPOX and FOLFOX. The committee were concerned that recommending a 3-month treatment length for both CAPOX and FOLFOX in line with the conclusions of the economic evidence may encourage an increased use of

CAPOX in patient groups where it may not be the most appropriate treatment. Patients may, even after explaining the toxicity risks, opt for 3-month CAPOX given the modest disease-free survival benefit from 3-month FOLFOX if an alternative of 6-month FOLFOX is not available. This is a higher risk group of Grade 3/4/5 diarrhoea with CAPOX chemotherapy. The committee noted during the recruitment of the SCOT trial 8 patients died in the CAPOX arm from diarrhoea and vomiting. Due to this the SCOT trial group specifically advised investigators on the management of severe diarrhoea in patients receiving CAPOX. The committee considered whether recommendations could be worded to prevent such crossover. The committee considered that doing so could go against the NICE technology appraisal on capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer (TA100). In particular the section on joint decision making when choosing the most appropriate treatment. It would also likely go against further principles of patient autonomy, consent and informed involvement in decision making.

Patients at high risk of severe chemotherapy-related diarrhoea may have worse quality of life outcomes, higher treatment-related morbidity and mortality and costs through treatment and hospitalisation from severe adverse events if they receive CAPOX. It is difficult to estimate a proportion, given this is not currently a decision faced in practise, but it would not be insignificant. This switch from FOLFOX to CAPOX was not considered in the economic evaluation. It would not have been picked up by ‘intention to treat’ as 6-month FOLFOX was available and clinical evidence was limited at the time.

The committee also consider that whilst 3-8 years follow-up was a long time in the context of an RCT, restricting the economic evaluation to this time horizon may underestimate the true lifetime costs for the 6-month group. This is an area with expensive downstream treatments and a patient group in which life expectancy is increasing. The clinical evidence review showed that disease-free survival was worse for 3 months FOLFOX chemotherapy than for 6 months FOLFOX (73.6% versus 76.0%, respectively, at 3 years), and that this result was statistically significant. Prolonged courses of expensive palliative treatments downstream may be forgone or delayed in patients if they remain disease free longer. This again will decrease the certainty around the cost effectiveness conclusions.

The committee concluded there was strong cost effectiveness evidence, based on strong clinical evidence for recommending a 3-month course of CAPOX chemotherapy. The committee acknowledge the strong economic evidence for a 3-month FOLFOX regimen however given the clinical concerns, it was decided that there should be an individualised consideration for the duration of FOLFOX for those who are not suitable for 3-month CAPOX chemotherapy, taking into account the benefits and short- and long-term harms of each option, and the person’s comorbidities and performance status and preference. The committee recognised that this approach favours individual values over population values and that there is potential for societal harm through inefficient allocation of resources.

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1 Appendices

2 Appendix A – Review protocol

3 Review protocol for review question: What is the optimal duration of adju-
4 vant chemotherapy for colorectal cancer

Field (based on PRISMA-P)	Content
Review question	What is the optimal duration of adjuvant chemotherapy for colorectal cancer?
Type of review question	Intervention
Objective of the review	Previous clinical trials have established 24 weeks of adjuvant chemotherapy to be the standard of care for colorectal cancer. In recent years a shorter duration of adjuvant chemotherapy have been suggested in order to minimise the adverse long-term effects of chemotherapy, mainly neurotoxicity. This review aims to find out what is the optimal duration of adjuvant chemotherapy for colorectal cancer taking into consideration its effects on for example survival and cancer recurrence, neurotoxicity and quality of life.
Eligibility criteria – population/disease/condition/issue/domain	Adults with non-metastatic colorectal cancer after receiving surgery with curative intent Non-metastatic cancer defined as: • pTany pN1-2 • pT3 • pT4 • M0 Subgroups to be considered separately: • pT4 • pT3/T4 N0 with vascular invasion • right versus left sided tumour • age over 70 years
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Adjuvant chemotherapy for less than 24 weeks (6 months), different durations analysed separately
Eligibility criteria – comparator(s)/control or reference (gold) standard	Adjuvant chemotherapy for 24 weeks (6 months) Studies that compare two durations shorter than 24 weeks to each other (for example 12 weeks versus 18 weeks) will also be considered and analysed separately.
Outcomes and prioritisation	**Critical outcomes:** • Disease-free survival (minimally important difference [MID]: statistical significance) • Overall survival (MID: statistical significance) • Neuropathy (lasting for 2 years considered permanent) (MID: statistical significance) **Important outcomes:**

Field (based on PRISMA-P)	Content
	• Overall quality of life measured using validated scales (MID: published MIDs from literature) • Distant metastasis (MID: statistical significance) • Treatment-related mortality (MID: statistical significance) • Dose reduction (MID: statistical significance) Quality of life MIDs from the literature: • EORTC QLQ-C30: 5 points* • EORTC QLQ-CR29: 5 points* • EORTC QLQ-CR38: 5 points* • EQ-5D: 0.09 using FACT-G quintiles • FACT-C: 5 points* • FACT-G: 5 points* • SF-12: > 3.77 for the mental component summary (MCS) and > 3.29 for the physical component summary (PCS) of the Short Form SF-12 (SF-12) • SF-36: > 7.1 for the physical functioning scale, > 4.9 for the bodily pain scale, and > 7.2 for the physical component summary *Confirmed with guideline committee.
Eligibility criteria – study design	Systematic reviews of randomised controlled trials (RCTs) RCTs Non-randomised studies will not be considered.
Other inclusion exclusion criteria	**Inclusion:** • English-language • Published full text papers • All settings will be considered that consider medications and treatments available in the UK • Studies published 2000 onwards Studies published 2000 onwards will be considered for this review question because the guideline committee considered that evidence prior to 2000 would not be relevant any longer because the duration of adjuvant chemotherapy for colorectal cancer used to be longer than the current standard of 24 weeks.
Proposed sensitivity/sub-group analysis, or meta-regression	In case of high heterogeneity, the following factors will be considered: • Type of chemotherapy
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Resolution of any disputes will be with the senior systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting will be undertaken for this question for a random 10% sample of the titles and abstracts identified by the search.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).

Field (based on PRISMA-P)	Content
	'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Potential sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews in first instance, but download all results Dates: from 2000
Identify if an update	Not an update
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10060 Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	For details please see appendix B.
Data items – define all variables to be collected	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for RCTs The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Pairwise meta-analysis of randomised trials will be conducted where appropriate. When meta-analysing continuous data, final and change scores will be pooled if baselines are comparable. If any studies report

Field (based on PRISMA-P)	Content
	both, the method used in the majority of studies will be analysed. Minimally important differences: The guideline committee identified statistically significant differences as appropriate indicators for clinical significance for all outcomes except for quality of life for which published MIDs from literature will be used (see outcomes section for more information).
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.
Confidence in cumulative evidence	For details see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Peter Hoskin in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplement 1: methods.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the NGA to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; EQ-5D: EuroQol five dimensions questionnaire; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Items; EORTC QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire colorectal cancer module (29 items); EORTC QLQ-CR38: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire colorectal cancer module (38 items); FACT-C: Functional Assessment of Cancer Therapy questionnaire (colorectal cancer); FACT-G: Functional Assessment of Cancer Therapy questionnaire (general); GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; M0: distant metastasis stage; MCS: mental component summary; MID: minimal important difference; N: nodal stage; NGA: National Guideline Alliance; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PCS: physical component summary; RCT: randomised controlled trial; RevMan5: Review Manager version 5; ROBIS: a tool for assessing risk of bias in systematic reviews; SF-12: 12-Item Short Form Survey; SF-36: 36-Item Short Form Survey; T: tumour stage

1 Appendix B – Literature search strategies

2 Literature search strategies for review question: What is the optimal duration of 3 adjuvant chemotherapy for colorectal cancer?

4 Database: Embase/Medline

5 Last searched on: 15/02/2019

#	Searches
1	exp Colorectal Neoplasms/
2	1 use prmz
3	exp colorectal tumor/ or colorectal cancer/
4	3 use oemezd
5	((colorect* or colo rect*) adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).ti,ab.
6	bowel cancer.ti,ab.
7	or/2,4-6
8	exp Antineoplastic Agents/ or exp Antineoplastic Protocols/ or exp Antineoplastic Combined Chemotherapy Protocols/ or exp Organoplatinum Compounds/ or exp Fluorouracil/ or exp Capecitabine/ or exp Chemotherapy, Adjuvant/ or exp Treatment Failure/ or exp Treatment Outcome/
9	8 use prmz
10	exp antineoplastic agent/ or exp clinical protocol/ or exp adjuvant chemotherapy/ or exp platinum complex/ or exp fluorouracil/ or exp capecitabine/ or exp oxaliplatin/ or exp capecitabine plus oxaliplatin/ or exp drug combination/ or exp drug efficacy/ or exp treatment response/ or exp cancer adjuvant therapy/ or exp cancer combination chemotherapy/ or exp treatment failure/ or exp clinical effectiveness/
11	10 use oemezd
12	(adjuvant chemotherap* or 5?FU or fluorouracil or capecitabine or oxaliplatin or XELOX or FOLFOX or FOLFIRI or XELIRI).ti,ab.
13	or/9,11-12
14	7 and 13
15	exp Time Factors/ use prmz
16	exp time factor/ or exp statistical significance/ or exp treatment duration/
17	16 use oemezd
18	(admin* or dose* or dosing* or dosage* or duration* or time* or course* or day* or month* or week*).ti,ab.
19	or/15,17-18
20	14 and 19
21	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
22	21 use prmz
23	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
24	23 use oemezd
25	or/22,24
26	20 and 25
27	(conference abstract or letter).pt. or letter/ or editorial.pt. or note.pt. or case report/ or case study/ use oemezd
28	Letter/ or editorial/ or news/ or historical article/ or anecdotes as topic/ or comment/ or case report/ use prmz
29	(letter or comment* or abstracts).ti.
30	or/27-29
31	randomized controlled trial/ use prmz
32	randomized controlled trial/ use oemezd
33	random*.ti,ab.
34	or/31-33
35	30 not 34
36	(animals/ not humans/) or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ use prmz
37	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ use oemezd
38	(rat or rats or mouse or mice).ti.
39	35 or 36 or 37 or 38
40	26 not 39
41	limit 40 to english language
42	limit 41 to yr="2000 -Current"

6

1 **Database: Cochrane Library**

2 Last searched on: 15/02/2019

#	Search
1	MeSH descriptor: [Colorectal Neoplasms] explode all trees
2	colorect* or colo rect*
3	#1 or #2
4	MeSH descriptor: [Antineoplastic Agents] explode all trees
5	MeSH descriptor: [Antineoplastic Protocols] explode all trees
6	MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees
7	MeSH descriptor: [Organoplatinum Compounds] explode all trees
8	MeSH descriptor: [Fluorouracil] explode all trees
9	MeSH descriptor: [Capecitabine] explode all trees
10	MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees
11	MeSH descriptor: [Treatment Failure] explode all trees
12	MeSH descriptor: [Treatment Outcome] explode all trees
13	adjuvant chemotherap* or 5?FU or fluorouracil or capecitabine or oxaliplatin or XELOX or FOLFOX or FOLFIRI or XELIRI
14	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or 13
15	MeSH descriptor: [Time Factors] explode all trees
16	admin* or dose* or dosing* or dosage* or duration* or time* or course* or day* or month* or week*
17	#15 or #16
18	#3 and #14 and #17 Publication Year from 2000 to 2018

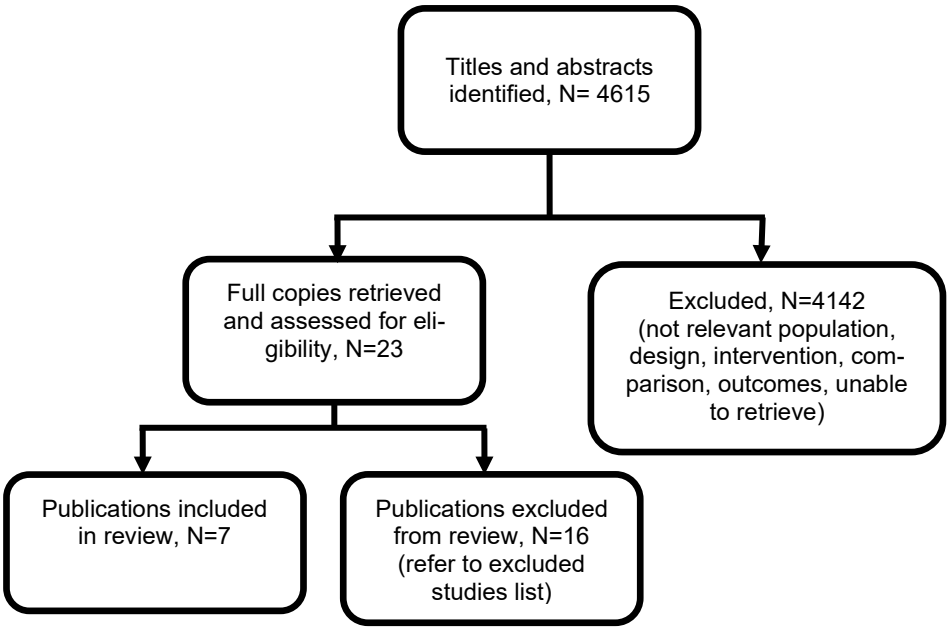
3

4

Appendix C – Clinical evidence study selection

Clinical study selection for review question: What is the optimal duration of adjuvant chemotherapy for colorectal cancer?

Figure 1: Study selection flow chart



1 Appendix D – Clinical evidence tables

2 Clinical evidence tables for review question: What is the optimal duration of adjuvant chemotherapy for colorectal cancer?

3 **Table 3: Clinical evidence tables**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Andre T, Vernerey D, Mineur L,, et al. (2018) Three Versus 6 Months of Oxaliplatin-Based Adjuvant Chemotherapy for Patients With Stage III Colon Cancer: Disease-Free Survival Results From a Randomized, Open-Label, International Duration Evaluation of Adjuvant (IDEA) France, Phase III Trial, J Clin Oncol, 36, 1469-1477 **Ref Id** 861108 **Country/ies where the study was carried out** France **Study type** RCT (IDEA France)	**Sample size** N=2,022 randomised; n=1,008 allocated to the 3-month therapy (n=900 received mFOLFOX6 and n=108 recevied CAPOX); n=1,014 assigned to the 6-month therapy (n=920 received mFOLFOX6 and n=94 received CAPOX) **Characteristics** Age in years, mean±SD 3 months 63.9±9.4 6 months 63.9±9.3 Male sex, n (%) 3 months 563 (56) 6 months 581 (58) Tumour stage, n (%) T1 3 months 45 (4) 6 months 33 (3)	**Interventions** 3 months of adjuvant chemotherapy versus 6 months of adjuvant chemotherapy Type of chemotherapy, n (%) Modified FOLFOX6 (infusional fluorouracil, leucovorin, and oxaliplatin for 6 or 12 cycles) 1,820 (90) CAPOX (capecitabine and oxaliplatin for four or eight cycles) 202 (10) The choice between modified FOLFOX6 and CAPOX was left to the patient and investigator decision.	**Details** Randomisation and allocation concealment Random allocation was done centrally via web, randomisation was stratified by centre, T stage, N stage, ECOG performance status, and age (<70 years or ≥70 years). Blinding No blinding. Follow-up/outcomes The primary endpoint was disease-free survival, defined as the time from random assignment to relapse or death, whichever occurred first (secondary colorectal cancers were regarded as events in the disease-free survival outcome, whereas	**Results** <u>Outcome: Overall survival (median 4.3 years of follow-up)</u> Whole population 3 months 145 events, n=1,002 6 months 129 events, n=1,008 HR 1.15 95% CI 0.91 to 1.46 Subpopulation who received mFOLFOX6 3 months 131 events, n=895 6 months 118 events, n=914 HR 1.16 95% CI 0.90 to 1.48 Subpopulation who received CAPOX 3 months 14 events, n=107	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: low risk Allocation concealment: unclear (Details not reported.) Performance bias Blinding of participants and personnel: unclear risk (No blinding, but unclear how much it would have an effect on performance.) Detection bias Blinding of outcome assessment: low/high (No blinding. For subjectively measured outcomes there could be a high risk of bias but low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To compare is a 3-month oxaliplatin-based adjuvant therapy is noninferior to the current 6-month standard treatment in patients with stage III colon cancer. **Study dates** May 12 2009 to May 21 2014 **Source of funding** French National Institute of Cancer; the French Ministry of Health by Program Hospitalier de Recherche Clinique 2009; Groupe Cooperateur Multidisciplinaire en Oncologie	T2 3 months 76 (8) 6 months 85 (8) T3 3 months 711 (71) 6 months 688 (68) T4 3 months 170 (17) 6 months 202 (20) Node stage, n (%) N0 3 months 1 (0.1) 6 months 2 (0.2) N1 3 months 748 (75) 6 months 753 (75) N2 3 months 253 (25) 6 months 253 (25) Tumour and node stage, n (%) T1-2 and N1 3 months 633 (63) 6 months 612 (61) T4 and/or N2 3 months 368 (37) 6 months 396 (39)		non-colorectal cancers were disregarded in the analysis). Secondary endpoints were overall survival, treatment compliance and toxicities. Peripheral sensory neuropathy was assessed during the whole study period. Residual peripheral sensory neuropathy was defined as the last available measurement for neuropathy toxicity. Maximal neuropathy was defined as the maximum grade observed at any study or follow-up period. **Statistical analysis** Analysis of the primary and secondary endpoints was performed on the basis of the modified intention-to-treat population (patients who did not receive any therapy whatsoever were excluded from the analysis, otherwise patients were analysed according to original randomisation).	6 months 11 events, n=94 HR 1.08 95% CI 0.49 to 2.37 <u>Outcome: Treatment-related mortality</u> 3 months 7/1,002 6 months 5/1,008 Disease-free survival, neuropathy and dose reduction from the IDEA France trial are reported within the pooled analysis of the IDEA collaboration trials in Grothey 2018.	risk of objective outcomes.) Attrition bias Incomplete outcome data: low risk Reporting bias Selective reporting: low risk Other bias Other sources of bias: - **Other information** None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Location of colon tumour, n (%) Left 3 months 569 (60) 6 months 592 (61) Right 3 months 377 (39) 6 months 369 (38) Both 3 months 8 (1) 6 months 8 (1) Missing 3 months 48 6 months 39 **Inclusion criteria** Age ≥ 18 years; stage III (according to TNM staging defined by the American Joint Cancer Committee); histologically confirmed colon cancer (tumour location greater than 12 cm from the anal verge by endoscopy and/or above the peritoneal reflection at surgery); had undergone curative intent surgery no more than 8 weeks before randomisation; without micro-				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	scopic evidence of residual disease; had an ECOG performance status of 0 or 1; had postoperative CEA levels ≤10 ng/mL (2 x normal value); and had signed written informed consent. Informed consent obtained before any study-specific procedures occurred. **Exclusion criteria** None reported.				
Full citation Chau I, Norman A, Cunningham D, et al. (2005) Longitudinal quality of life and quality adjusted survival in a randomised controlled trial comparing six months of bolus fluorouracil/leucovorin vs. twelve weeks of protracted venous infusion fluorouracil as adjuvant chemotherapy for colorectal cancer, European Journal of Cancer, 41, 1551-1559 **Ref Id** 860893	**Sample size** See Chau et al. (2005) A randomised comparison between 6 months of bolus fluorouracil/leucovorin and 12 weeks of protracted venous infusion fluorouracil as adjuvant treatment in colorectal cancer. Annals of oncology: official journal of the European society for medical oncology, 16, 549-557 **Characteristics** **Inclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information** None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out **Study type** **Aim of the study** **Study dates** **Source of funding**	**Exclusion criteria**				
Full citation Chau I, Norman A, Cunningham D, et al. (2005) A randomised comparison between 6 months of bolus fluorouracil/leucovorin and 12 weeks of protracted venous infusion fluorouracil as adjuvant treatment in colorectal cancer. Annals of oncology 16, 549-557 **Ref Id** 836561 **Country/ies where the study was carried out** UK **Study type** Multicentre RCT	**Sample size** N=826 randomised; n=411 allocated to 12 weeks 5-FU infusion; n=415 allocated to 6 months of bolus 5-FU/leucovorin **Characteristics** Age in years, median (range) 12 weeks 5-FU infusion 63 (27-82) 6 months bolus 5-FU/leucovorin 62 (28-95) Male sex, n (%) 12 weeks 5-FU infusion 211 (53) 6 months bolus 5-FU/leucovorin 220 (55)	**Interventions** 12 weeks of protracted venous infusion of 5-FU versus bolus 5-FU/leucovorin for 6 months Protracted venous infusion of 5-FU was administered at a dose of 300 mg/m2 per day for 12 weeks. Bolus 5-FU 425 mg/m2 and leucovorin 20 mg/m2 were administered on days 1–5 every 4 weeks for six cycles. (Patients aged >70 years were treated with a reduced starting dose of 370 mg/m2.) Adjuvant radiotherapy was given to patients	**Details** Randomisation and allocation concealment Randomisation was done by an independent randomisation office on 1:1 ratio using random permuted blocks. Randomisation was stratified by treatment centre and in cases of rectal cancer, whether preoperative radiotherapy was given. Blinding No blinding. Follow-up/outcomes Follow-up was done every 3 months for the first year, every 6 months for the second	**Results** Outcome: Relapse-free survival (median 65 months of follow-up; event is cancer recurrence or development of metachronous primary colorectal cancer) Whole population 12 weeks 5-FU infusion 104 events, n=397 6 months bolus 5-FU/leucovorin 127 events, n=404 HR 0.8 95% CI 0.62 to 1.04, p=0.1 Subpopulation with rectal cancer 12 weeks 5-FU infusion 39 events, n=156	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: low risk Allocation concealment: unclear risk (Details not reported.) Performance bias Blinding of participants and personnel: unclear risk (No blinding, unclear how much lack of blinding could affect performance of clinicians, probably low risk.) Detection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To compare the efficacy and toxicity of 12 weeks of protracted venous infusion 5-fluorouracil (5-FU) against the standard bolus monthly regimen of 5-FU/leucovorin given for 6 months as adjuvant treatment in colorectal cancer. **Study dates** 1993 to 2003 **Source of funding** Not reported.	Site of primary tumour Colon 12 weeks 5-FU infusion 241 (61) 6 months bolus 5-FU/leucovorin 237 (59) Rectum 12 weeks 5-FU infusion 156 (39) 6 months bolus 5-FU/leucovorin 167 (41) Duke's stage (colon cancer) B 12 weeks 5-FU infusion 105 (44) 6 months bolus 5-FU/leucovorin 106 (45) C 12 weeks 5-FU infusion 135 (56) 6 months bolus 5-FU/leucovorin 131 (55) Duke's stage (rectal cancer) B 12 weeks 5-FU infusion 58 (37)	with T4 tumour considered to be at high risk of locoregional failure, and was planned to start with the fourth cycle of bolus therapy or after completion of 12 weeks of protracted venous infusion 5-FU, which continued at a reduced dose of 200 mg/m2 until completion of radiotherapy.	year and annually thereafter. Serum CEA was measured at baseline and at each clinic visit. Computer tomography scans of the thorax, abdomen and pelvis were performed at baseline, and at 12 and 24 months following initial start of chemotherapy. Colonoscopy was recommended at 12 months after the start of chemotherapy, subsequent colonoscopies was left to the surgeons' discretion. The primary outcome was overall survival, defined as the time from the date of randomisation to the date of death from any cause. Secondary end points were relapse-free survival (defined as the time from the date of randomisation to the date of either cancer recurrence or development of metachronous primary colorectal cancer), toxicity and quality of life. Quality of life was	6 months bolus 5-FU/leucovorin 59 events, n=167 HR 0.63 95% CI 0.43 to 0.94, p=0.0246 <u>Outcome: Overall survival (median 65 months of follow-up; event is death from any cause)</u> Whole population 12 weeks 5-FU infusion 99 events, n=397 6 months bolus 5-FU/leucovorin 121 events, n=404 HR 0.79 95% CI 0.61 to 1.03, p=0.083* Note * calculated values used in the forest plot and corresponding GRADE table are different due to rounding (0.78 [95% CI 0.60, 1.02]) Subpopulation with rectal cancer 12 weeks 5-FU infusion, n=156 (number of events not reported)	Blinding of outcome assessment: high/low risk (No blinding. Potentially high risk of bias due to lack of blinding for subjective outcomes but low risk of objective outcomes.) Attrition bias Incomplete outcome data: low risk Reporting bias Selective reporting: low risk Other bias Other sources of bias: - **Other information** None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	6 months bolus 5-FU/leucovorin 95 (61) C 12 weeks 5-FU infusion 56 (34) 6 months bolus 5-FU/leucovorin 109 (65) Radiotherapy received (rectal cancer) Preoperative 12 weeks 5-FU infusion 9 (6) 6 months bolus 5-FU/leucovorin 16 (10) Postoperative 12 weeks 5-FU infusion 24 (15) 6 months bolus 5-FU/leucovorin 10 (6) **Inclusion criteria** Curatively resected stage II and III adenocarcinoma of the colon or rectum; resection margins clear by at least 1 mm; adequate haematological, renal and liver function; no concurrent severe or life-threatening illness.		assessed using the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) before randomisation, during adjuvant treatment and during follow-up. **Statistical analysis** Analysis was on intention-to-treat basis (although in total 25 participants were excluded from the analysis after randomisation due to ineligibility). Survival was analysed using the Kaplan–Meier method and were compared between treatment groups using the log-rank test, stratified by treatment centre.	6 months bolus 5-FU/leucovorin, n=167 (number of events not reported) HR 0.66 95% CI 0.43 to 1.03, p=0.0697 <u>Outcome: Quality of life - Global health status (QLQ-C30; scale 0-100; higher score indicating better quality of life)</u> Change score from baseline at 24 weeks post-randomisation** 12 weeks 5-FU infusion 5.6 (n not reported) 6 months bolus 5-FU/leucovorin 2.2 (n not reported) p<0.001 Change score from baseline at 2 years post-randomisation* 12 weeks 5-FU infusion 9.3 (n not reported) 6 months bolus 5-FU/leucovorin 9.0 (n not reported) p=0.999 <u>Outcome: Distant metastasis</u>	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Metastatic disease			12 weeks 5-FU infusion 84/397 6 months bolus 5-FU/leucovorin 97/404 Outcome: Chemotherapy-related mortality 12 weeks 5-FU infusion 0/397 6 months bolus 5-FU/leucovorin 0/404 Outcome: Dose reduction - percentage of dose received 12 weeks 5-FU infusion 90% 6 months bolus 5-FU/leucovorin 74% p<0.001 Outcome: Dose reduction - percentage of patients with completed treatment (no dose reductions, delayed or interruptions) 12 weeks 5-FU infusion 45.7% 6 months bolus 5-FU/leucovorin 13.3%	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				*Data extracted from Chau, Norman et al. 2005. ** Data extracted from Saini 2003.	
Full citation Grothey A, Sobrero A, Shields A, et al. (2018) Duration of Adjuvant Chemotherapy for Stage III Colon Cancer, N Engl J Med, 378, 1177-1188 **Ref Id** 860602 **Country/ies where the study was carried out** Australia, Canada, Denmark, France, Greece, Italy, Japan, New Zealand, Spain, Sweden, UK, US **Study type** Pooled analysis from 6 collaborating RCTs (IDEA collaboration): TOSCA (Italy) N=2,402 SCOT (UK, Denmark, Spain, Australia, Sweden, New Zealand) N=3,983 IDEA France N=2,010	**Sample size** N=12,834 randomised; n=6,424 allocated to the 3-month group (n=3,870 received FOLFOX and n=2,554 received CAPOX); n=6,410 allocated to the 6-month group (n=3,893 received FOLFOX and n=2,517 received CAPOX) **Characteristics** Age in years, median (range): 64 (18-88) Male sex, n (%): 7,243 (56) Tumour stage, n (%): T1 493 (4) T2 1,197 (9) T3 8,400 (66) T4 2,655 (21) Missing 89 (1)	**Interventions** 3 months of adjuvant chemotherapy versus 6 months of adjuvant chemotherapy Chemotherapy regimen, n (%): Capecitabine and oxaliplatin (CAPOX) 5,071 (39.5) Fluorouracil, leucovorin, and oxaliplatin (FOLFOX) 7,763 (60.5) The choice of chemotherapy regimen was non-randomised and made by the treating physicians.	**Details** Randomisation and allocation concealment Randomisation method and allocation concealment for individual trials not reported. However, reports from the individual trials give more detail and appropriate methods were applied. Blinding No blinding. Follow-up/outcomes Primary outcome was disease-free survival at 3 years, defined as the time from randomisation to first relapse, the diagnosis of a secondary colorectal cancer after the initial diagnosis, or death from any cause, whichever occurred first. **Statistical analysis**	**Results** <u>Outcome: Disease-free survival at 3 years (median 41.8 months of follow-up)</u> Whole population 3 months 74.6% (95% CI 73.5% to 75.7%) (n=6,424) 6 months 75.5% (95% CI 74.4% to 76.7%) (n=6,410) HR 1.07 95% CI 1.00 to 1.15 Subpopulation who received CAPOX 3 months 75.9% (95% CI 74.2% to 77.6%) (n=2,554) 6 months 74.8% (95% CI 73.1% to 76.6%) (n=2,517) HR 0.95 95% CI 0.85 to 1.06	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (The paper did not report methods of randomisation for individual trials, however, the reports and/or protocols from 3 of the 6 individual trials report sufficient detail to confirm appropriate methods were used.) Allocation concealment: unclear risk (The paper did not report methods of allocation concealment for individual trials, however, the reports and/or protocols from 3 of the 6 individual trials report sufficient detail to confirm appropriate methods were used.)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
CALGB/SWOG (US, Canada) N=2,440 HORG (Greece) N=708 ACHIEVE (Japan) N=1,291 **Aim of the study** To evaluate if 3 months of FOLFOX or CAPOX therapy would be non-inferior to 6 months of therapy in the rate of disease-free survival at 3 years. **Study dates** June 2007 to December 2015 **Source of funding** National Cancer Institute; Institute National du Cancer; Programme Hospitalier de Recherche Clinique en Cancérologie; the National Institute for Health Research, Efficacy and Mechanism Evaluation; the National Institute for Health Research; Health Technology Assessment; Cancer Research United Kingdom; the Japanese	Nodal stage, n (%): N1 9,168 (71) N2 3,567 (28) Missing 99 (1) Risk group, n (%): T1, T2, or T3N1 7,471 (59) T4, N2, or both 5,256 (41) **Inclusion criteria** Patients with stage III colon cancer (individual trials might have had slightly differing inclusion criteria) **Exclusion criteria** None reported.		Modified intention-to-treat analysis was performed (included all the patients who were randomised and had received at least one dose of a trial drug). Cox regression model stratified according to each trial was used to estimate hazard ratios and 95% CI for the comparison of 3 months versus 6 months of adjuvant chemotherapy.	Subpopulation who received FOLFOX 3 months 73.6% (95% CI 72.2% to 75.1%) (n=3,870) 6 months 76.0% (95% CI 74.6% to 77.5%) (n=3,893) HR 1.16 95% CI 1.06 to 1.26 Subpopulation with T4 cancer 3 months 58.1% 6 months 61.4% HR 1.16 95% CI 1.03 to 1.31 Subpopulation with T1-3 N1 cancer (low risk population) 3 months 83.1% (95% CI 81.8% to 84.4%) 6 months 83.3% (95% CI 82.1% to 84.6%) HR 1.01 95% CI 0.90 to 1.12* Note: * calculated values used in the forest plot and corresponding GRADE table differ due to rounding (1.01 [95% CI 0.9, 1.13])	Performance bias Blinding of participants and personnel: high/unclear risk (No blinding, unclear how much lack of blinding could affect performance of clinicians, probably low risk.) Detection bias Blinding of outcome assessment: high/unclear risk (No blinding. Potentially high risk of bias due to lack of blinding for subjective outcomes but low risk of objective outcomes.) Attrition bias Incomplete outcome data: low risk Reporting bias Selective reporting: low risk Other bias Other sources of bias: The inclusion/exclusion criteria as well as the details of the Interventions differ to an extent

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Foundation for Multidisciplinary Cancer Treatment; L'Agenzia Italiana del Farmaco; the HORG Foundation.				Subpopulation with T1-3 N1 cancer (low risk population) who received CAPOX 3 months 85.0 (95% CI 83.1% to 86.9%) 6 months 83.1% (95% CI 81.1% to 85.2%) HR 0.85 95% CI 0.71 to 1.01 Subpopulation with T1-3 N1 cancer (low risk population) who received FOLFOX 3 months 81.9% (95% CI 80.2% to 83.6%) 6 months 83.5% (95% CI 81.9% to 85.1%) HR 1.10 95% CI 0.96 to 1.26 Subpopulation with T4 and/or N2 cancer (high risk population) 3 months 62.7% (95% CI 60.8% to 64.4%) 6 months 64.4% (95% CI 62.6% to 66.4%) HR 1.12 95% CI 1.03 to 1.23	across the 6 different individual trials pooled in this collaborative paper. A BIT MORE TO BE ADDED ABOUT DIFFERENCES BETWEEN THE TRIALS. The 6 trials are also different in size accounting for unequal amount of weight in the analysis. The SCOT trial is the largest of the trials with almost 4,000 participants, TOSCA and CALGB/SWOG both had around 2,400 participants, IDEA France trial had around 2,000 participants, ACHIEVE trial has around 1,300 participants while HORG had around 700 participants. **Other information** None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Subpopulation with T4 and/or N2 cancer (high risk population) who received CAPOX 3 months 64.1% (95% CI 61.3% to 67.1%) 6 months 64.0% (95% CI 61.2% to 67.0%) HR 1.02 95% CI 0.89 to 1.17 Subpopulation with T4 and/or N2 cancer (high risk population) who received FOLFOX 3 months 61.5% (95% CI 58.9% to 64.1%) 6 months 64.7% (95% CI 62.2% to 67.3%) HR 1.20 95% CI 1.07 to 1.35 <u>Outcome: Grade 3 or 4 peripheral sensory neurotoxicity</u> Whole population 3 months 117/6,424 6 months 643/6,410 Subpopulation who received CAPOX 3 months 37/2,554	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				6 months 124/2,517 Subpopulation who received FOLFOX 3 months 80/3,870 6 months 519/3,893 <u>Outcome: Dose reduction - Percentage of dose delivered, mean ± SD</u> Subpopulation who received FOLFOX Fluorouracil 3 months 92.4 ± 22.7 (n=3,870) 6 months 81.6 ± 26.6 (n=3,893) Oxaliplatin 3 months 91.4 ± 19.9 (n=3,870) 6 months 72.8 ± 25.6 (n=3,893) Subpopulation who received CAPOX Capecitabine 3 months 91.2 ± 23.5 (n=2,554) 6 months 78.0 ± 29.4 (n=2,517)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Oxaliplatin 3 months 89.8 ± 21.7 (n=2,554) 6 months 69.3 ± 28.3 (n=2,517)	
Full citation Iveson T, Kerr R, Saunders M, et al. (2018) 3 versus 6 months of adjuvant oxaliplatin-fluoropyrimidine combination therapy for colorectal cancer (SCOT): an international, randomised, phase 3, non-inferiority trial. Lancet Oncology 19: 562-578 **Ref Id** 860452 **Country/ies where the study was carried out** UK, Denmark, Spain, Sweden, Australia, and New Zealand **Study type** RCT (SCOT) **Aim of the study** To investigate whether 3 months of oxaliplatin-containing chemother-	**Sample size** N=6,088 randomised; n=3,044 allocated to 3-month therapy; n=3,044 allocated to 6-month therapy **Characteristics** Age in years, median (IQR) 3 months 65 (58-70) 6 months 65 (58-70) Male sex, n (%) 3 months 1843 (61) 6 months 1844 (61) Disease site, n (%) Colon 3 months 2492 (82) 6 months 2144 (70) Rectum 3 months 552 (28) 6 months 549 (18) T stage, n (%) T0	**Interventions** 3 months of adjuvant chemotherapy versus 6 months of adjuvant chemotherapy Type of chemotherapy, n (%) FOLFOX (bolus and infused fluorouracil with oxaliplatin) 3 months 993 (33) 6 months 988 (32) CAPOX (capecitabine and oxaliplatin) 3 months 2,051 (67) 6 months 2,056 (68) The choice of the type of chemotherapy was not randomised but was chosen by the treating physician and patient. FOLFOX was given every 2 weeks (i.e. 6 or 12 cycles depending on	**Details** Randomisation and allocation concealment Randomisation was done centrally via computer system in 1:1 ratio, stratified by centre, choice of chemotherapy, sex, disease site, N stage and T stage, and if the patient was going to receive CAPOX the starting dose of capecitabine. Once enrolled, patients were randomly assigned via computer programme and allocated a unique identification number. Blinding No blinding. Follow-up/outcomes The primary outcome was disease-free survival, defined as the time from randomisation	**Results** Outcome: Disease-free survival (median 37 months of follow-up) Subpopulation with rectal cancer 3 months 107 events, n=551 6 months 114 events, n=547 HR 0.926 95% CI 0.711 to 1.205 Outcome: Overall survival (median 37 months of follow-up) 3 months 393 events, n=3,035 6 months 394 events, n=3,030 HR 0.994 95% CI 0.964 to 1.143 Outcome: Quality of life - QLQ-C30 global health status (scale 0-	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: low risk Allocation concealment: low risk Performance bias Blinding of participants and personnel: unclear risk (No blinding, unclear how much lack of blinding could affect performance of clinicians, probably low risk.) Detection bias Blinding of outcome assessment: high/low risk (No blinding. Potentially high risk of bias due to lack of blinding for subjective outcomes but low risk of objective outcomes.)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
apy would be non-inferior to the usual 6 months of treatment. **Study dates** March 27 2008 to Nov 29 2013 **Source of funding** Medical Research Council; Swedish Cancer Society; Cancer Research UK Core Clinical Trials Unit Funding; NHS Greater Glasgow & Clyde; University of Glasgow	3 months 1 (<1) 6 months 3 (<1) T1 3 months 92 (30 6 months 95 (3) T2 3 months 284 (9) 6 months 283 (9) T3 3 months 1749 (57) 6 months 1748 (57) T4 3 months 917 (30) 6 months 915 (30) N stage, n (%) N0 3 months 559 (18) 6 months 557 (18) N1 3 months 1731 (57) 6 months 1732 (57) N2 3 months 754 (25) 6 months 755 (25) High risk stage II*, n (%) 3 months 551 (18) 6 months 545 (81)	the allocation). IV oxaliplatin 85 mg/m² was given over 2 hours on the first day concurrently with L-folinic acid 175 mg or folinic acid (leucovorin) 350 mg. This was followed by an IV bolus injection of fluorouracil 400 mg/m² over 5 minutes, then a continuous IV infusion of fluorouracil 2400 mg/m² over 46 hours. CAPOX was given every 3 weeks (i.e. 4 or 8 cycles depending on the allocation). IV oxaliplatin 130 mg/m² was given on the first day over 2 hours. Oral capecitabine 1000 mg/m² was taken twice per day for the first 14 days of each cycle. (Patients older than 70 years of age could be given 75% of the capecitabine full dose if deemed appropriate depending on the fitness of the patient.)	(or trial registration for those randomised after 3 months of therapy) to relapse, development of a new colorectal cancer, or death from any cause. Secondary endpoints were overall survival (defined as the time from randomisation (registration for those randomised at 3 months) to death from any cause), safety, quality of life and cost-effectiveness. Quality of life was assessed with the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-CR29 and EQ-5D-3L (visual analogue scale and health index). The quality of life questionnaires were administered at baseline and before each treatment cycle, each month in the 3 month group for the first 3 months after treatment, and at months 9 and 12 for the EORTC questionnaires and months 9, 12, 18,	100, higher score indicating better quality of life) At 6 months Mean difference in score between groups (3 months minus 6 months) 11.58 (95% CI 9.62 to 13.54), p<0.001 At 12 months Mean difference in score between groups (3 months minus 6 months) 1.48 (95% CI -0.19 to 3.14), p>0.05 Outcome: Quality of life - EQ-5D visual analogue scale At 6 months Mean difference in score between groups (3 months minus 6 months) 9.80 (SE 1.04), p<0.001 At 12 months Mean difference in score between groups (3 months minus 6 months) 1.45 (SE 0.88), p>0.05 Outcome: Treatment-related mortality	Attrition bias Incomplete outcome data: low risk Reporting bias Selective reporting: low risk Other bias Other sources of bias: - **Other information** None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	*defined as one or more of the following: T4 disease, tumour obstruction with or without perforation of the primary tumour preoperatively, fewer than ten lymph nodes harvested, poorly differentiated histology, perineural invasion, or extramural venous or lymphatic vascular invasion. **Inclusion criteria** Aged ≥18 years; had undergone a curative resection for stage III or high-risk stage II* adenocarcinoma of the colon or rectum; WHO performance status 0 or 1; adequate organ function; life expectancy of greater than 5 years with reference to non-cancer related diseases; normal CT scan of the chest, abdomen, and pelvis before study enrolment; carcinoembryonic antigen less than 1.2 times the local upper limit of normal within 1 week before		and 24, then annually for EQ-5D-3L. Neuropathy was assessed with the FACT/GOG-Ntx4 questionnaire. **Statistical analysis** Analysis was done on intention-to-treat population as much as possible. Kaplan-Meier techniques and Cox proportional hazard ratios were used to analyse disease-free survival and overall survival.	3 months 16/3,035 6 months 16/3,030 Disease-free survival, neuropathy, and dose reduction among people with colon cancer from the SCOT trial are reported within the pooled analysis of the IDEA collaboration trials in Grothey 2018.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	randomisation; patients with rectal cancer had to have undergone total mesorectal excision surgery with negative resection margins (defined as >1 mm clearance). *defined as having one or more of the following: T4 disease, tumour obstruction with or without perforation of the primary tumour preoperatively, fewer than ten lymph nodes harvested, poorly differentiated histology, perineural invasion, or extramural venous or lymphatic vascular invasion **Exclusion criteria** Chemotherapy (except if administered with curative intent and completed >5 years ago and from which there were no residual complications); previous long-course chemoradiotherapy (preoperative short-course radiotherapy alone was allowed);				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	moderate or severe renal impairment (glomerular filtration rate or creatinine clearance <30 mL/min, as calculated with the Cockcroft-Gault equation); haemoglobin less than 9 g/dL; absolute neutrophil count less than 1.5 x 10^9/L; platelet count <100 x 10^9/L; aspartate aminotransferase or alanine aminotransferase greater than 2.5 times the upper limit of normal; clinically significant cardiovascular disease; pregnancy or lactation or being of child-bearing potential and not using, or willing to use, medically approved contraception (postmenopausal women must have been amenorrhoeic for at least 12 months to be considered of non-childbearing potential); previous malignancy other than adequately treated in-situ carcinoma of the uterine cervix or basal or squamous cell carcinoma of the skin (unless there				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	had been a disease-free interval of at least 5 years); known or suspected dihydropyrimidine dehydrogenase deficiency.				
Full citation Lonardi S, Sobrero A, Rosati G, et al. (2016) Phase III trial comparing 3-6 months of adjuvant FOLFOX4/XELOX in stage II-III colon cancer: safety and compliance in the TOSCA trial, Annals of Oncology 27: 2074-2081 **Ref Id** 859553 **Country/ies where the study was carried out** Italy **Study type** RCT (TOSCA) **Aim of the study** To evaluate the efficacy and safety of a shorter course of treatment in radically resected stage II/III colon cancer patients.	**Sample size** N=3,759 randomised; n=1,870 allocated to 3 months adjuvant chemotherapy; n=1,889 allocated to 6 months adjuvant chemotherapy **Characteristics** Age in years, mean (range) 3 months 63.4 (21-83) 6 months 63.1 (21-84) Male sex, n (%) 3 months 1,035 (56) 6 months 1,027 (55) Stage, n (%) II 3 months 641 (35) 6 months 648 (35) III 3 months 1,207 (65) 6 months 1,219 (65)	**Interventions** 3-month adjuvant chemotherapy versus 6-month adjuvant chemotherapy Type of chemotherapy FOLFOX4 (oxaliplatin and 5-FU) 3 months 64% 6 months 64% CAPOX (capecitabine and oxaliplatin) 36% 3 month 36% 6 months 36% FOLFOX4 therapy was administered as IV infusion of oxapliplatin 85 mg/m2 over 2 hours, concurrently with LV 100 mg/m2, followed by 5-FU 400 mg/m2 as bolus injection and 5-FU 600 mg/m2 as IV infusion over 22 hours on the first day. On day 2, LV 100 mg/m2, 5-FU	**Details** Randomisation and allocation concealment Randomisation was done centrally at Mario Negri Institute with the use of permuted blocks of variable size, randomisation was stratified by centre and cancer stage. Blinding No blinding. Follow-up/outcomes Follow-up visits happened every 4 months during the first 3 years after completion of study treatment phase and annually after that. Laboratory assessment and abdominal ultrasound were carried out, and a yearly abdominal CT scan and chest X-ray were required as a	**Results** Outcome: Treatment-related mortality (within 30 days) 3 months 3/1,820 6 months 7/1,834 Disease-free survival and neuropathy from the TOSCA trial are reported within the pooled analysis of the IDEA collaboration trials in Grothey 2018.	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: low risk Allocation concealment: low risk Performance bias Blinding of participants and personnel: unclear risk (No blinding, unclear how much lack of blinding could affect performance of clinicians, probably low risk.) Detection bias Blinding of outcome assessment: high/low risk (No blinding. Potentially high risk of bias due to lack of blinding for subjective outcomes but low risk of objective outcomes.)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates June 2007 to March 2013 **Source of funding** Agenzia Italiana del Farmaco	T stage, n (%) Tx 3 months 7 (0.4) 6 months 5 (0.3) T0 3 months 0 (0) 6 months 2 (0.1) T1 3 months 33 (1.8) 6 months 44 (2.4) T2a 3 months 74 (4) 6 months 98 (5) T2b 3 months 43 (2.4) 6 months 35 (1.9) T3 3 months 1,391 (76) 6 months 1,358 (73) T4 3 months 285 (16) 6 months 313 (17) Unknown 3 months 15 6 months 12 N stage, n (%) Nx 3 months 4 (0.2) 6 months 9 (0.5) N0	400mg/m2 bolus injection, and 5-FU 600 mg/m2 IV infusion over 22 hours were administered as previous day. Cycles were repeated every 2 weeks (i.e. either 6 or 12 cycles depending on the allocation). CAPOX therapy was administered as IV infusion of oxaliplatin 130 mg/m2 over 2 hours on the first day, followed by oral capecitabine 1000 mg/m2 twice daily on day 1–14. Cycles were repeated every 3 weeks (i.e. 4 or 8 cycles depending on the allocation).	minimum. Colonoscopies were carried out within 1 year from surgery, and every 3–5 years after that (if negative). Toxicities and treatment modifications were recorded during treatment. Primary outcome was relapse-free survival, defined as time from date of randomisation up to date of first relapse or death from any cause. Secondary outcomes were overall survival and safety. **Statistical analysis** Analysis for safety outcomes was done on modified intention-to-treat population (defined as all randomised patients without major violations of eligibility criteria).		Attrition bias Incomplete outcome data: low risk Reporting bias Selective reporting: low risk Other bias Other sources of bias: - **Other information** None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	3 months 623 (34) 6 months 362 (34) N1 3 months 869 (48) 6 months 895 (48) N2 3 months 4 (0.2) 6 months 3 (0.2) N3 3 months 4 (0.2) 6 months 3 (0.2) Unknown 3 months 21 6 months 15 **Inclusion criteria** Histologically confirmed stage III or high-risk stage II (fulfilling at least 1 of the following criteria: T4 tumour, grade >3, onset with bowel obstruction/perforation, vascular or lymphatic/perineural invasion, <12 nodes examined) colon cancer; age >18 years; curative surgery carried out no less than 3 and no more than 10 weeks before randomisation; ECOG performance status ≤1;				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	signed written informed consent. **Exclusion criteria** Macroscopic or microscopic evidence of residual tumour; prior cytotoxic chemotherapy/radiotherapy/immunotherapy for colon cancer; other malignancies within the last 5 years; lactating women; history/presence of other dysfunction or clinical laboratory findings suggesting a disease or condition that contraindicates experimental therapy or high risk of treatment complications; chronic daily treatment with high-dose aspirin (>325 mg/day).				
Full citation Saini A, Norman A, Cunningham D, et al. (2003) Twelve weeks of protracted venous infusion of fluorouracil (5-FU) is as effective as 6 months of bolus 5-FU and folinic acid as adjuvant treat-	**Sample size** See Chau et al. (2005) A randomised comparison between 6 months of bolus fluorouracil/leucovorin and 12 weeks of protracted venous infusion fluorouracil as adjuvant treatment in colorectal cancer. Annals of	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
ment in colorectal cancer, British Journal of Cancer 88: 1859-1865 **Ref Id** 859983 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	oncology: official journal of the european society for medical oncology, 16, 549-557 **Characteristics** **Inclusion criteria** Exclusion criteria				

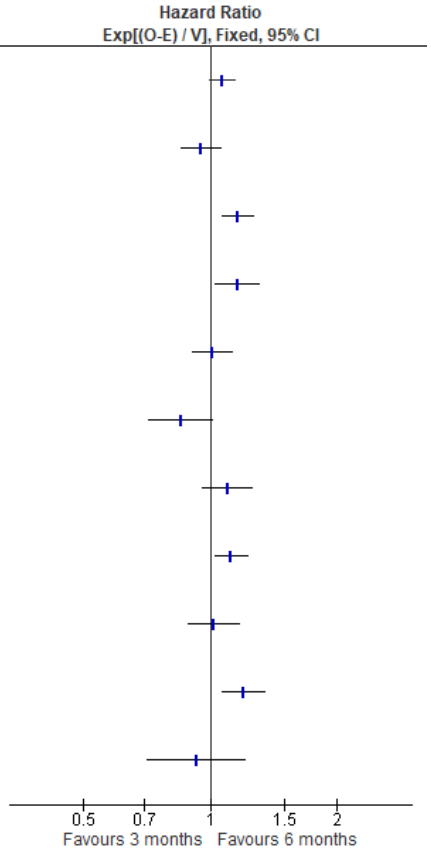
5-FU: fluorouracil; CAPOX: capecitabine and oxaliplatin; CEA: carcinoembryonic antigen; CI: confidence interval; CT: computer tomography; ECOG: Eastern Cooperative Oncology Group; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: EuroQol five dimensions; FACT/GOG-Ntx4: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity questionnaire; FOLFOX: folinic acid, fluorouracil and oxaliplatin; HR: hazard ratio; IQR: interquartile range; IV: intravenous; LV: leucovorin; N: nodal stage; NHS: National Health Service; QLQ-C30: Quality of Life Questionnaire Core 30 Items; QLQ-CR29: Quality of Life Questionnaire colorectal cancer module (29 items); RCT: randomised controlled trial; SD: standard deviation; SE: standard error; T: tumour stage; TNM: tumour, node and metastasis

Appendix E – Forest plots

Forest plots for review question: What is the optimal duration of adjuvant chemotherapy for colorectal cancer?

Figure 2: Comparison 1: 3 months versus 6 months of oxaliplatin-based adjuvant chemotherapy for non-metastatic colorectal cancer – Disease-free survival (follow-up median 3.5 years for all subgroups except for rectal cancer population (follow up median 3.1years); event is relapse, diagnosis of secondary colorectal cancer or death from any cause

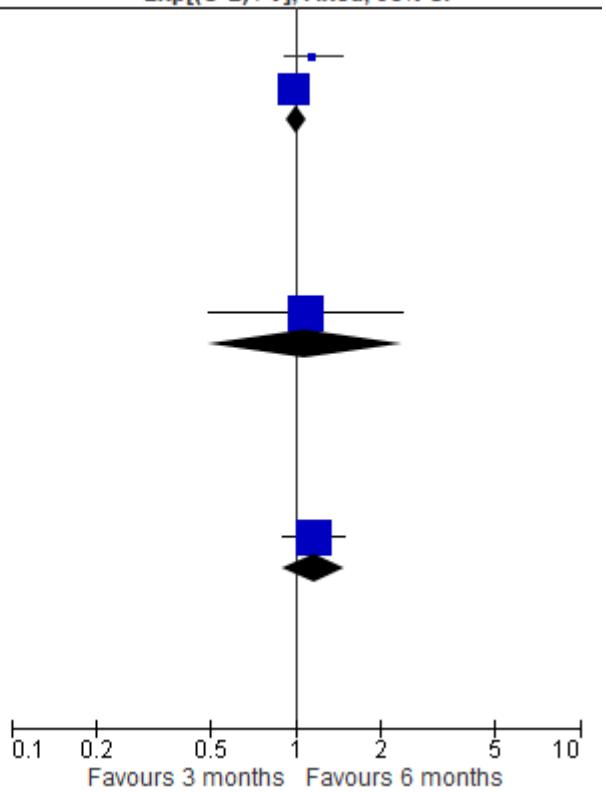
Study or Subgroup	3 months Events	3 months Total	6 months Events	6 months Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.1.1 Whole population (colon cancer)							
IDEA collaboration (Grothey 2018)	0	6424	0	6410	53.22	786.64	1.07 [1.00, 1.15]
1.1.2 Subpopulation who received CAPOX (colon cancer)							
IDEA collaboration (Grothey 2018)	0	2554	0	2517	-16.17	315.21	0.95 [0.85, 1.06]
1.1.3 Subpopulation who received FOLFOX (colon cancer)							
IDEA collaboration (Grothey 2018)	0	3870	0	3893	76.64	514.34	1.16 [1.06, 1.27]
1.1.4 Subpopulation with stage T4 colon cancer							
IDEA collaboration (Grothey 2018)	0	0	0	0	39.44	265.73	1.16 [1.03, 1.31]
1.1.5 Subpopulation with stage T1-3 N1 (low risk) colon cancer							
IDEA collaboration (Grothey 2018)	0	0	0	0	3.2	321.29	1.01 [0.91, 1.13]
1.1.6 Subpopulation wth stage T1-3 N1 (low risk) colon cancer who received CAPOX							
IDEA collaboration (Grothey 2018)	0	0	0	0	-20.1	123.7	0.85 [0.71, 1.01]
1.1.7 Subpopulation with stage T1-3 N1 (low risk) colon cancer who received FOLFOX							
IDEA collaboration (Grothey 2018)	0	0	0	0	19.8	207.79	1.10 [0.96, 1.26]
1.1.8 Subpopulation with stage T4 and/or N2 (high risk) colon cancer							
IDEA collaboration (Grothey 2018)	0	0	0	0	55.3	487.95	1.12 [1.02, 1.22]
1.1.9 Subpopulation with stage T4 and/or N2 (high risk) colon cancer who received CAPOX							
IDEA collaboration (Grothey 2018)	0	0	0	0	4.07	205.36	1.02 [0.89, 1.17]
1.1.10 Subpopulation with stage T4 and/or N2 (high risk) colon cancer who received FOLFOX							
IDEA collaboration (Grothey 2018)	0	0	0	0	51.85	284.39	1.20 [1.07, 1.35]
1.1.11 Subpopulation with rectal cancer							
SCOT trial (Iveson 2018)	107	551	114	547	-4.24	55.21	0.93 [0.71, 1.21]



CAPOX: cabecitabine and oxaliplatin; CI: confidence interval; FOLFOX: folinic acid, fluorouracil and oxaliplatin; N: nodal stage; O-E: observed minus expected; T: tumour stage; V: variance

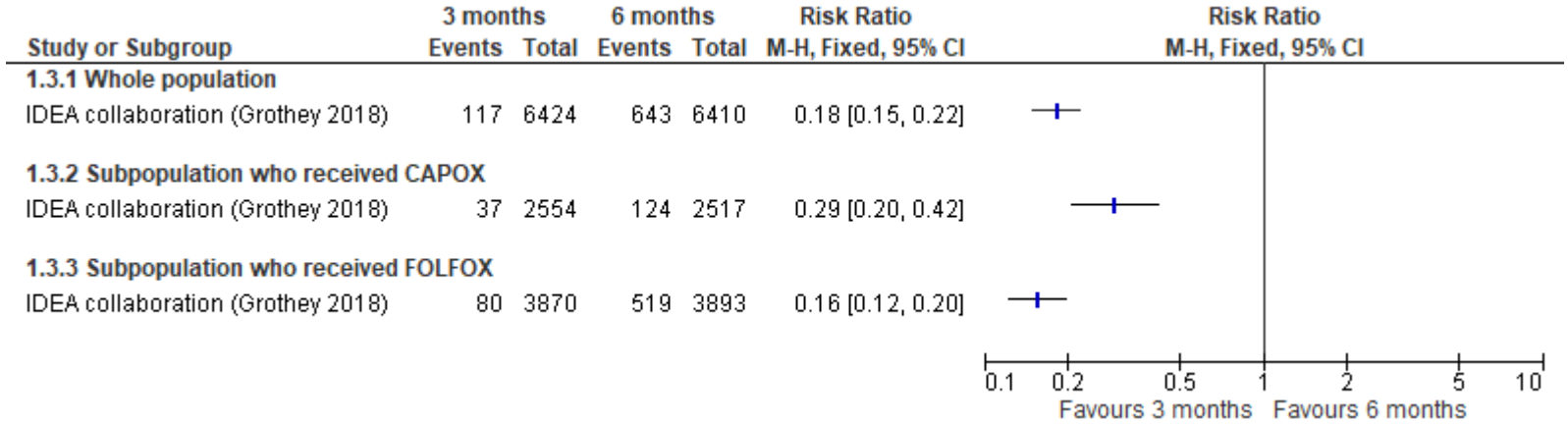
Figure 3: Comparison 1: 3 months versus 6 months of oxaliplatin-based adjuvant chemotherapy for non-metastatic colorectal cancer – Overall survival (follow-up median 3.1 to 4.3 years); event is death from any cause

Study or Subgroup	3 months Events	3 months Total	6 months Events	6 months Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.2.1 Whole population								
IDEA France trial (Andre 2018)	145	1002	129	1008	9.61	68.75	11.5%	1.15 [0.91, 1.46]
SCOT trial (Iveson 2018)	393	3035	394	3030	-3.19	529.69	88.5%	0.99 [0.91, 1.08]
Subtotal (95% CI)		**4037**		**4038**			**100.0%**	**1.01 [0.93, 1.10]**
Total events	538		523					
Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² = 23%								
Test for overall effect: Z = 0.26 (P = 0.79)								
1.2.2 Subpopulation who received CAPOX								
IDEA France trial (Andre 2018)	14	107	11	94	0.48	6.18	100.0%	1.08 [0.49, 2.38]
Subtotal (95% CI)		**107**		**94**			**100.0%**	**1.08 [0.49, 2.38]**
Total events	14		11					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.19 (P = 0.85)								
1.2.3 Subpopulation who received FOLFOX								
IDEA France trial (Andre 2018)	131	895	118	914	9.22	62.11	100.0%	1.16 [0.90, 1.49]
Subtotal (95% CI)		**895**		**914**			**100.0%**	**1.16 [0.90, 1.49]**
Total events	131		118					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.17 (P = 0.24)								



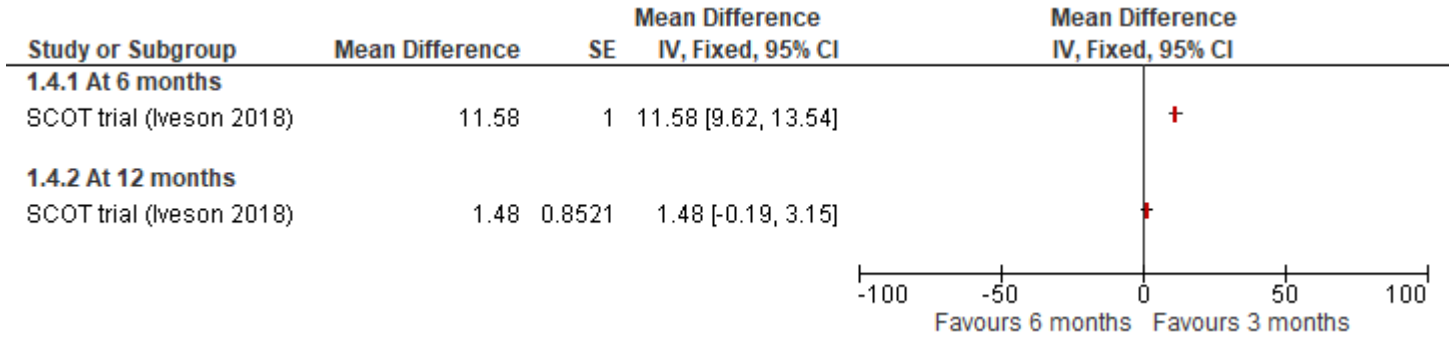
CAPOX: capecitabine and oxaliplatin; CI: confidence interval; FOLFOX: folinic acid, fluorouracil and oxaliplatin; O-E: observed minus expected; V: variance

Figure 4: Comparison 1: 3 months versus 6 months of oxaliplatin-based adjuvant chemotherapy for non-metastatic colorectal cancer – Grade 3 or 4 peripheral neuropathy (maximal level at any time point after randomisation)



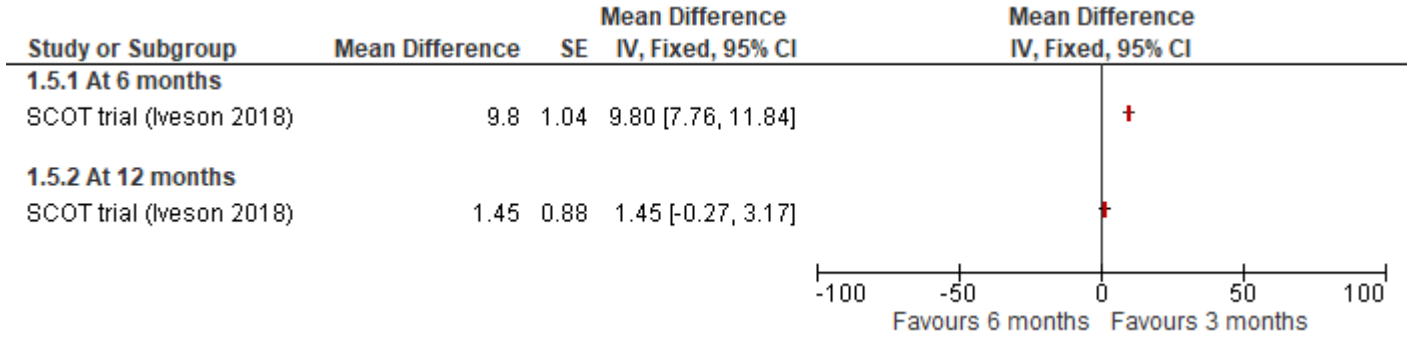
CAPOX: cabecitabine and oxaliplatin; CI: confidence interval; FOLFOX: folinic acid, fluorouracil and oxaliplatin; M-H: Mantel-Haenszel

Figure 5: Comparison 1: 3 months versus 6 months of oxaliplatin-based adjuvant chemotherapy for non-metastatic colorectal cancer – Quality of life – QLQ-C30 global health status (scale 0-100; better indicated by higher values)



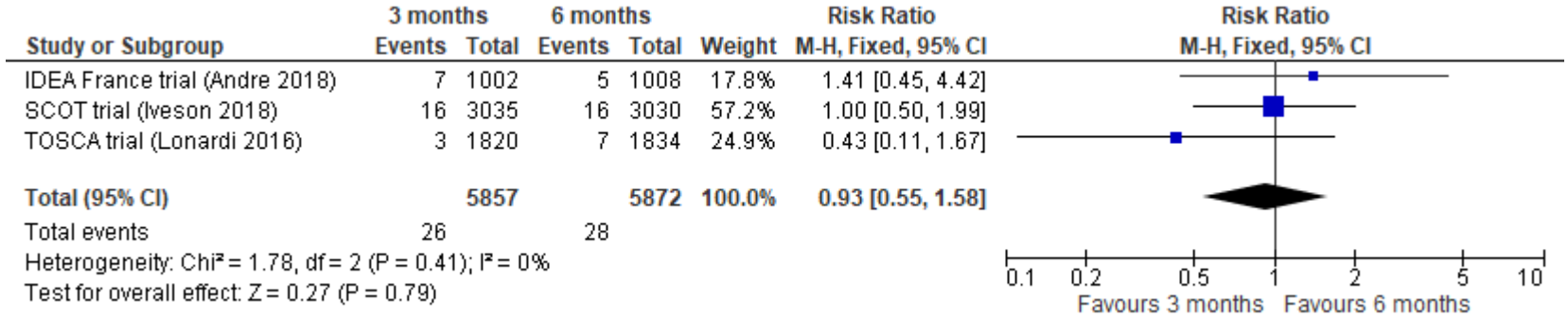
CI: confidence interval; IV: inverse variance; QLQ-C30: Quality of Life Questionnaire Core 30 Items; SE: standard error

Figure 6: Comparison 1: 3 months versus 6 months of oxaliplatin-based adjuvant chemotherapy for non-metastatic colorectal cancer – Quality of life – EQ-5D VAS (scale 0-100; better indicated by higher values)



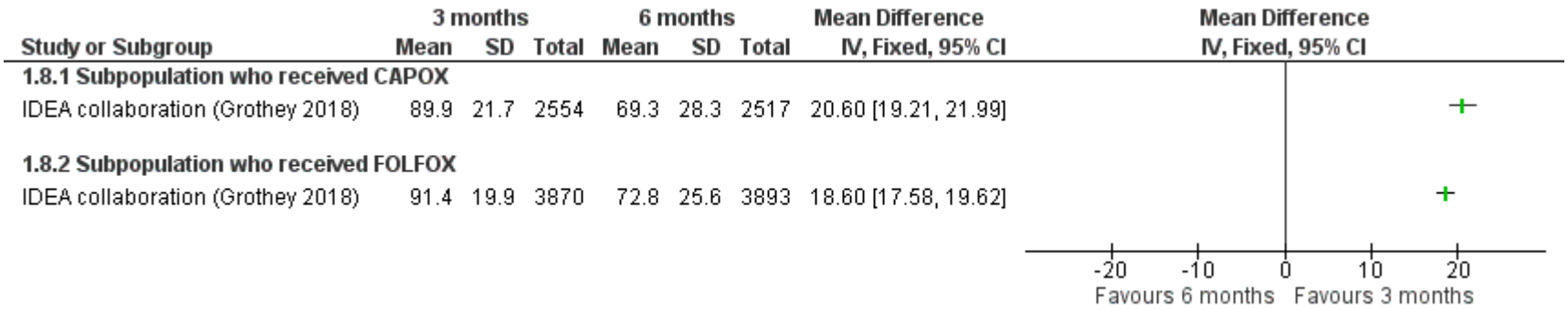
CI: confidence interval; EQ-5D VAS: EuroQol five dimensions visual analogue scale; IV: inverse variance; SE: standard error

Figure 7: Comparison 1: 3 months versus 6 months of oxaliplatin-based adjuvant chemotherapy for non-metastatic colorectal cancer – Treatment-related mortality



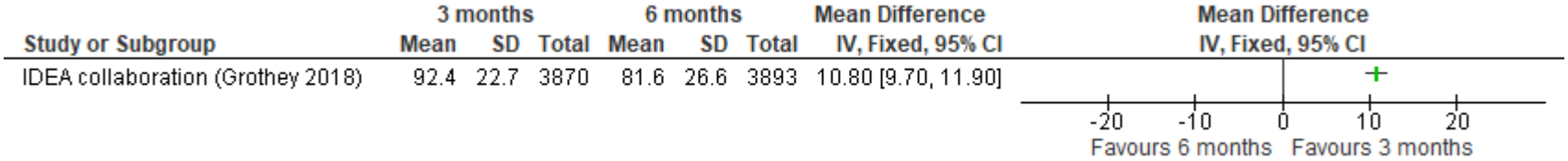
CI: confidence interval; M-H: Mantel-Haenszel

Figure 8: Comparison 1: 3 months versus 6 months of oxaliplatin-based adjuvant chemotherapy for non-metastatic colorectal cancer – Percentage of oxaliplatin dose delivered (better indicated by higher values)



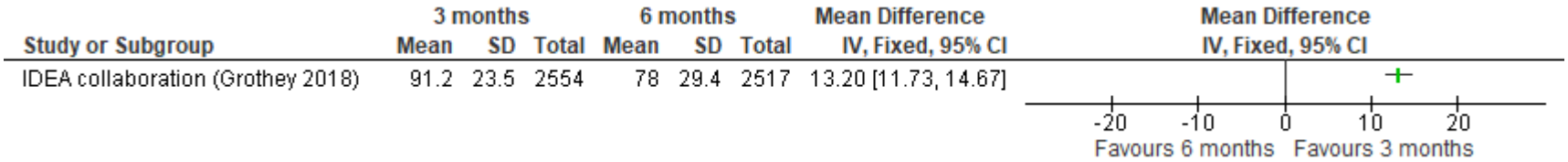
CAPOX: cabecitabine and oxaliplatin; CI: confidence interval; FOLFOX: folinic acid, fluorouracil and oxaliplatin; IV: inverse variance; SD: standard deviation

Figure 9: Comparison 1: 3 months versus 6 months of oxaliplatin-based adjuvant chemotherapy for non-metastatic colorectal cancer – Percentage of fluorouracil dose delivered (FOLFOX subpopulation) (better indicated by higher values)



CI: confidence interval; FOLFOX: folinic acid, fluorouracil and oxaliplatin; IV: inverse variance; SD: standard deviation

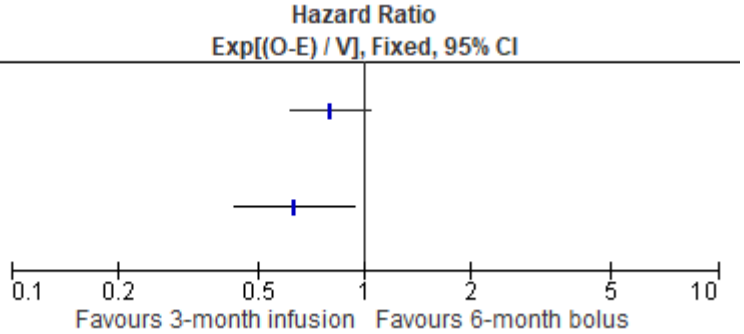
Figure 10: Comparison 1: 3 months versus 6 months of oxaliplatin-based adjuvant chemotherapy for non-metastatic colorectal cancer – Percentage of capecitabine dose delivered (CAPOX subpopulation) (better indicated by higher values)



CAPOX: capecitabine and oxaliplatin; CI: confidence interval; IV: inverse variance; SD: standard deviation

Figure 11: Comparison 2: 3 months of fluorouracil infusion versus 6 months of bolus fluorouracil and leucovorin – Disease-free survival (follow-up median 5.4 years for whole population, median 4.6 years for rectal cancer population); event is cancer recurrence or development of metachronous primary colorectal cancer

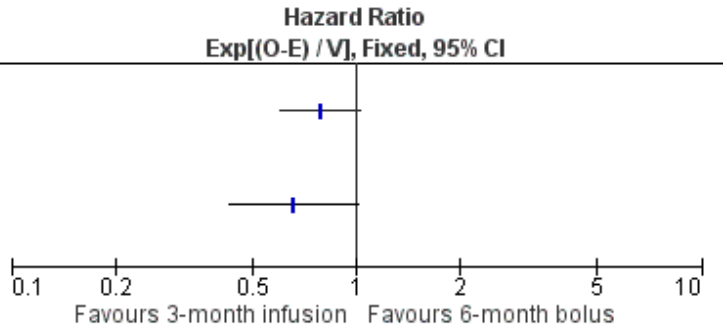
Study or Subgroup	3-month infusion Events	Total	6-month bolus Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
2.1.1 Whole population							
Chau 2005	104	397	127	404	-12.82	57.43	0.80 [0.62, 1.04]
2.1.2 Subpopulation with rectal cancer							
Chau 2005	39	156	59	167	-11.61	25.12	0.63 [0.43, 0.93]



CI: confidence interval; O-E: observed minus expected; V: variance

Figure 12: Comparison 2: 3 months of fluorouracil infusion versus 6 months of bolus fluorouracil and leucovorin – Overall survival (follow-up median 5.4 years for whole population, median 4.6 years for rectal cancer population)); event is cancer recurrence or development of metachronous primary colorectal cancer

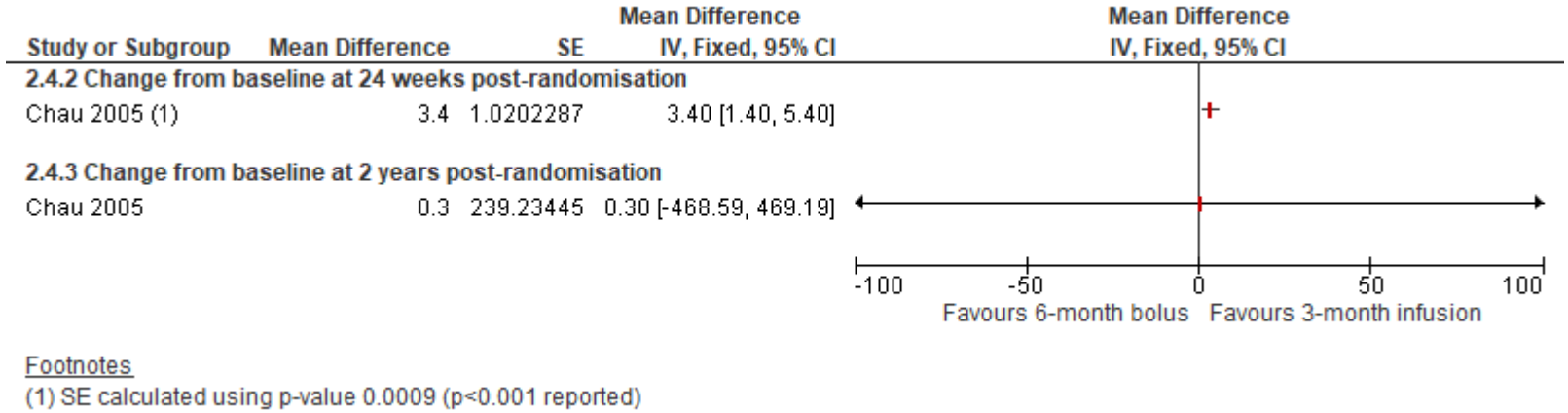
Study or Subgroup	3-month infusion Events	Total	6-month bolus Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
2.2.1 Whole population							
Chau 2005	99	397	121	404	-13.2	54.45	0.78 [0.60, 1.02]
2.2.2 Subpopulation with rectal cancer							
Chau 2005 (1)	0	156	0	167	-8.56	20.59	0.66 [0.43, 1.02]



Footnotes
(1) Number of events not reported.

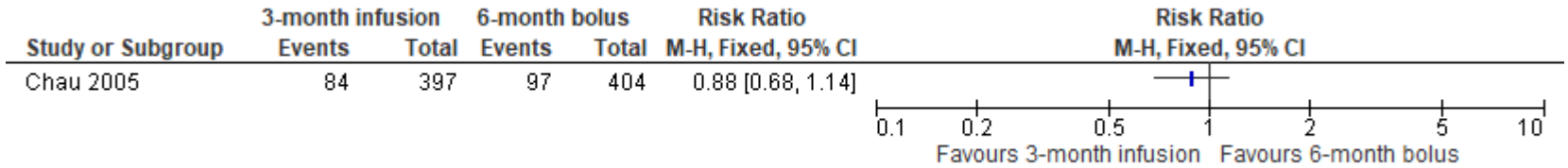
CI: confidence interval; O-E: observed minus expected; V: variance

Figure 13: Comparison 2: 3 months of fluorouracil infusion versus 6 months of bolus fluorouracil and leucovorin – Quality of life – QLQ-C30 global health status (scale 0-100; better indicated by higher values)



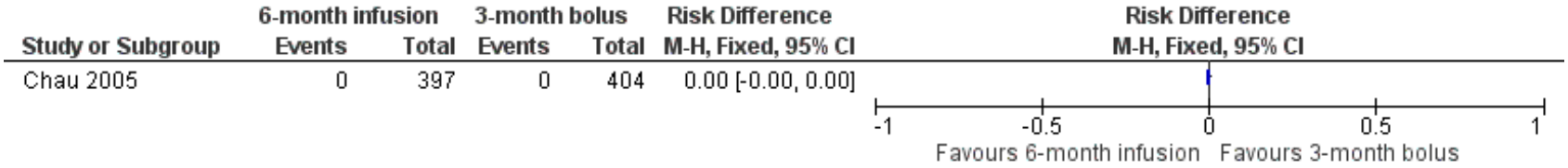
CI: confidence interval; IV: inverse variance; QLQ-C30: Quality of Life Questionnaire Core 30 items; SE: standard error

Figure 14: Comparison 2: 3 months of fluorouracil infusion versus 6 months of bolus fluorouracil and leucovorin – Distant metastasis (follow-up median 5.4 years)



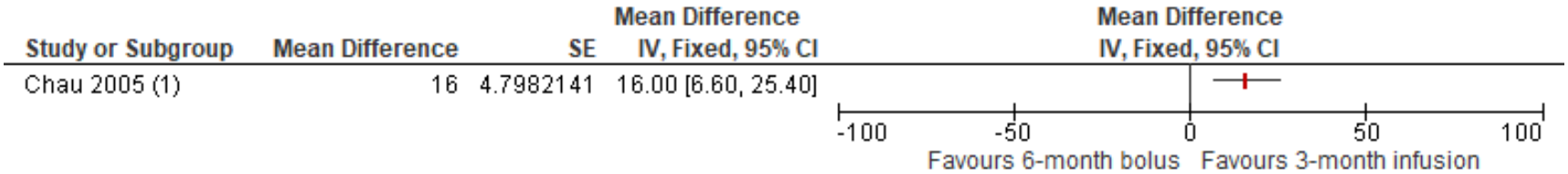
CI: confidence interval; M-H: Mantel-Haenszel

Figure 15: Comparison 2: 3 months of fluorouracil infusion versus 6 months of bolus fluorouracil and leucovorin – Chemotherapy-related mortality



CI: confidence interval; M-H: Mantel-Haenszel

Figure 16: Comparison 2: 3 months of fluorouracil infusion versus 6 months of bolus fluorouracil and leucovorin – Percentage of dose delivered (Better indicated by higher values)



Footnotes
(1) SE calculated using p-value 0.0009 (p<0.001 reported)

CI: confidence interval; IV: inverse variance; SE: standard error

Appendix F – GRADE tables

GRADE tables for review question: What is the optimal duration of adjuvant chemotherapy for non-metastatic colorectal cancer?

Table 4: Clinical evidence profile: Comparison 1: 3 months versus 6 months of oxaliplatin-based adjuvant chemotherapy for colorectal cancer

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months	6 months	Relative (95% CI)	Absolute	Quality	Importance
Disease-free survival - Whole population (follow-up median 3.5 years; event is relapse, diagnosis of secondary colorectal cancer or death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	6424 (number of events not reported, 3263 across both arms)	6410 (number of events not reported, 3263 across both arms)	HR 1.07 (1.00 to 1.15)	At 3 years for 6-month arm 75.5%[1], for 3-month arm 74.6% (73.5% to 75.7%)	HIGH	CRITICAL
Disease-free survival - Subpopulation who received CAPOX (follow-up median 3.5 years; event is relapse, diagnosis of secondary colorectal cancer or death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2554 (number of events not reported, 1299 across both arms)	2517 (number of events not reported, 1299 across both arms)	HR 0.95 (0.85 to 1.06)	At 3 years for 6-month arm 74.8%[1], for 3-month arm 75.9% (74.2% to 77.6%)	HIGH	CRITICAL
Disease-free survival - Subpopulation who received FOLFOX (follow-up median 3.5 years; event is relapse, diagnosis of secondary colorectal cancer or death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3870 (number of events not reported, 1964 across both arms)	3893 (number of events not reported, 1964 across both arms)	HR 1.16 (1.06 to 1.27)	At 3 years for 6-month arm 76.0%[1], for 3-month arm 73.6% (72.2% to 75.1%)	HIGH	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months	6 months	Relative (95% CI)	Absolute	Quality	Importance
Disease-free survival - Subpopulation with stage T4 cancer (follow-up median 3.5 years; event is relapse, diagnosis of secondary colorectal cancer or death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported (2655 patients with 1075 events across both arms)	Not reported (2655 patients with 1075 events across both arms)	HR 1.16 (1.03 to 1.31)	At 3 years for 6-month arm 61.4%, for 3-month arm 56.8% (52.8% to 60.5%)[2]	HIGH	CRITICAL
Disease-free survival - Subpopulation with stage T1-3 N1 (low risk) cancer (follow-up median 3.5 years; event is relapse, diagnosis of secondary colorectal cancer or death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported (7471 patients with 1313 events across both arms)	Not reported (7471 patients with 1313 events across both arms)	HR 1.01 (0.91 to 1.13)	At 3 years for 6-month arm 83.3%[1], for 3-month arm 83.1% (81.8% to 84.4%)	HIGH	CRITICAL
Disease-free survival - Subpopulation with stage T1-3 N1 cancer who received CAPOX (follow-up median 3.5 years; event is relapse, diagnosis of secondary colorectal cancer or death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	HR 0.85 (0.71 to 1.01)	At 3 years for 6-month arm 83.1%[1], for 3-month arm 85.0% (83.1% to 86.9%)	HIGH	CRITICAL
Disease-free survival - Subpopulation with stage T1-3 N1 (low risk) cancer who received FOLFOX (follow-up median 3.5 years; event is relapse, diagnosis of secondary colorectal cancer or death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	HR 1.10 (0.96 to 1.26)	At 3 years for 6-month arm 83.5%[1], for 3-month arm 81.9% (80.2% to 83.6%)	HIGH	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months	6 months	Relative (95% CI)	Absolute	Quality	Importance
Disease-free survival - Subpopulation with stage T4 and/or N2 (high risk) cancer (follow-up median 3.5 years; event is relapse, diagnosis of secondary colorectal cancer or death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported (5256 patients with 1935 events across both arms)	Not reported (5256 patients with 1935 events across both arms)	HR 1.12 (1.02 to 1.22)	At 3 years for 6-month arm 64.4%[1], for 3-month arm 62.7% (60.8% to 64.4%)	HIGH	CRITICAL
Disease-free survival - Subpopulation with stage T4 and/or N2 (high risk) cancer who received CAPOX (follow-up median 3.5 years; event is relapse, diagnosis of secondary colorectal cancer or death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	HR 1.02 (0.89 to 1.17)	At 3 years for 6-month arm 64.0%[1], for 3-month arm 64.1% (61.3% to 67.1%)	HIGH	CRITICAL
Disease-free survival - Subpopulation with stage T4 and/or N2 (high risk) cancer who received FOLFOX (follow-up median 3.5 years; event is relapse, diagnosis of secondary colorectal cancer or death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	HR 1.20 (1.07 to 1.35)	At 3 years for 6-month arm 64.7%[1], for 3-month arm 61.5% (58.9% to 64.1%)	HIGH	CRITICAL
Disease-free survival - Subpopulation with rectal cancer (follow-up median 3.1 years; event is relapse, diagnosis of secondary colorectal cancer or death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	107/551 (19.4%)	114/547 (20.8%)	HR 0.93 (0.71 to 1.21)	At 3 years for 6-month arm 77%[4], for 3-month arm 78.5% (73% to 83%)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months	6 months	Relative (95% CI)	Absolute	Quality	Importance
Overall survival - Whole population (follow-up median 3.1 to 4.3 years; event is death from any cause)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	538/4037 (13.3%)	523/4038 (13%)	HR 1.01 (0.93 to 1.10)	At 3 years for 6-month arm 90.0%[5], for 3-month arm 89.9% (89.1% to 90.7%)	HIGH	CRITICAL
Overall survival - Subpopulation who received CAPOX (follow-up median 4.3 years; event is death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	14/107 (13.1%)	11/94 (11.7%)	HR 1.08 (0.49 to 2.38)	At 3 years for 6-month arm 89%[6], for 3-month arm 92% (85% to 96%)	MODERATE	CRITICAL
Overall survival - Subpopulation who received FOLFOX (follow-up median 4.3 years; event is death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	131/895 (14.6%)	118/914 (12.9%)	HR 1.16 (0.90 to 1.49)	At 3 years for 6-month arm 93%[6], for 3-month arm 91% (89% to 93%)	MODERATE	CRITICAL
Grade 3 or 4 peripheral neuropathy - Whole population (maximal level at any time point after randomisation)												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	117/6424 (1.8%)	643/6410 (10%)	RR 0.18 (0.15 to 0.22)	82 fewer per 1000 (from 78 fewer to 85 fewer)	MODERATE	CRITICAL
Grade 3 or 4 peripheral neuropathy - Subpopulation who received CAPOX (maximal level at any time point after randomisation)												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/2554 (1.4%)	124/2517 (4.9%)	RR 0.29 (0.20 to 0.42)	35 fewer per 1000 (from 29 fewer to 39 fewer)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**3 months**	**6 months**	**Relative (95% CI)**	**Absolute**		
Grade 3 or 4 peripheral neuropathy - Subpopulation who received FOLFOX (maximal level at any time point after randomisation)												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	80/3870 (2.1%)	519/3893 (13.3%)	RR 0.16 (0.12 to 0.20)	112 fewer per 1000 (from 107 fewer to 117 fewer)	MODERATE	CRITICAL
Quality of life - global health status (QLQ-C30) – Change from baseline at 6 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	-	MD 11.58 higher (9.62 to 13.54 higher)	MODERATE	IMPORTANT
Quality of life - global health status (QLQ-C30) – Change from baseline at 12 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	-	MD 1.48 higher (0.19 lower to 3.15 higher)	MODERATE	IMPORTANT
Quality of life - EQ-5D VAS - Change from baseline at 6 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision[8]	none	Not reported	Not reported	-	MD 9.80 higher (7.76 to 11.84 higher)	MODERATE	IMPORTANT
Quality of life - EQ-5D VAS - Change from baseline at 12 months (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	-	MD 1.45 higher (0.27 lower to 3.17 higher)	MODERATE	IMPORTANT
Distant metastasis												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Treatment-related mortality												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	26/5857 (0.44%)	28/5872 (0.48%)	RR 0.93 (0.55 to 1.58)	0 fewer per 1000 (from 2 fewer to 3 more)	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months	6 months	Relative (95% CI)	Absolute	Quality	Importance
Percentage of oxaliplatin dose delivered - Subpopulation who received CAPOX (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2554	2517	-	MD 20.60 higher (19.21 to 21.99 higher)	HIGH	IMPORTANT
Percentage of oxaliplatin dose delivered - Subpopulation who received FOLFOX (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3870	3893	-	MD 18.60 higher (17.58 to 19.62 higher)	HIGH	IMPORTANT
Percentage of fluorouracil dose delivered (FOLFOX subpopulation) (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3870	3893	-	MD 10.80 higher (9.70 to 11.90 higher)	HIGH	IMPORTANT
Percentage of capecitabine dose delivered (CAPOX subpopulation) (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2554	2517	-	MD 13.20 higher (11.73 to 14.67 higher)	HIGH	IMPORTANT

CAPOX: cabecitabine and oxaliplatin; CI: confidence interval; EQ-5D VAS: EuroQol five dimensions questionnaire visual analogue scale; FOLFOX: folinic acid, fluorouracil and oxaliplatin; HR: hazard ratio; MD: mean difference; N: nodal stage; QLQ-C30: Quality of life questionnaire Core 30 items; RR: relative risk; T: tumour stage

1 From IDEA Collaboration (Grothey 2018).

2 Calculated from the control group survival and HR.

3 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (less than 300 events).

4 Estimated from the whole population in the SCOT trial (Iveson 2018).

5 Estimated from SCOT trial (Iveson 2018) and IDEA France trial (Andre 2018).

6 From IDEA France trial (Andre 2018).

7 Quality of evidence downgraded by 1 because of no of blinding.

8 Imprecision estimated based on the MID for EQ-5D VAS scale 0-100 being 5.

Table 5: Clinical evidence profile: Comparison 2: 3 months of fluorouracil infusion versus 6 months of bolus fluorouracil and leucovorin

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months fluorouracil infusion	6 months bolus fluorouracil/leucovorin	Relative (95% CI)	Absolute	Quality	Importance
Disease-free survival - Whole population (follow-up median 5.4 years; event is cancer recurrence or development of metachronous primary colorectal cancer)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	104/397 (26.2%)	127/404 (31.4%)	HR 0.80 (0.62 to 1.04)	At 5 years for 6-month arm 66.7%[2], for 3-month arm 73.3% (68.4% to 77.6%)[3]	MODERATE	CRITICAL
Disease-free survival - Subpopulation with rectal cancer (follow-up median 4.6 years; event is cancer recurrence or development of metachronous primary colorectal cancer)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	39/156 (25%)	59/167 (35.3%)	HR 0.63 (0.43 to 0.93)	At 5 years for 6-month arm 57.7%[2], for 3-month arm 74% (65.5% to 80.7%)	MODERATE	CRITICAL
Overall survival - Whole population (follow-up median 5.4 years; event is death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	99/397 (24.9%)	121/404 (30%)	HR 0.78 (0.60 to 1.02)	At 5 years for 6-month arm 71.5%[2], for 3-month arm 75.7% (70.8% to 79.9%)	MODERATE	CRITICAL
Overall survival - Subpopulation with rectal cancer (follow-up median 4.6 years; event is death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	156	167	HR 0.66 (0.43 to 1.02)	At 5 years for 6-month arm 65.3%[2], for 3-month arm 78.8% (70.2% to 85.1%)[3]	MODERATE	CRITICAL
Neuropathy												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 months fluorouracil infusion	6 months bolus fluorouracil/leucovorin	Relative (95% CI)	Absolute	Quality	Importance
Quality of life - global health status (QLQ-C30) - Change from baseline at 24 weeks post-randomisation (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	Not reported	Not reported	-	MD 3.40 higher (1.40 to 5.40 higher)	LOW	IMPORTANT
Quality of life - global health status (QLQ-C30) - Change from baseline at 2 years post-randomisation (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[6]	none	Not reported	Not reported	-	MD 0.30 higher (468.59 lower to 469.19 higher)	VERY LOW	IMPORTANT
Distant metastasis (follow-up median 5.4 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	84/397 (21.2%)	97/404 (24%)	RR 0.88 (0.68 to 1.14)	29 fewer per 1000 (from 77 fewer to 34 more)	MODERATE	IMPORTANT
Chemotherapy-related mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Not estimable[7]	none	0/397 (0%)	0/404 (0%)	RD 0,00 (-0.00, 0.00)	-[7]	HIGH	IMPORTANT
Percentage of dose delivered (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	342	350	-	MD 16.00 higher (6.60 to 25.40 higher)	HIGH	IMPORTANT

CI: confidence interval; HR: hazard ratio; MD: mean difference; QLQ-C30: Quality of Life Questionnaire core 30 items; RD: risk difference; RR: relative risk

1 Quality of evidence was downgraded by 1 because of imprecision of the effect estimate (less than 300 events).

2 From Chau 2005a.

3 Although there appears to be difference at 5 years, as reported in the paper, overall the HR was not significantly different so there was unlikely to be a clinically important difference.

4 Quality of evidence was downgraded by 1 because of no blinding.

5 Quality of evidence was downgraded by 1 because the 95% CI of the absolute effect crosses 1 MID.

6 Quality of evidence was downgraded by 2 because the 95% CI of the absolute effect crosses 2 MIDs.

7 Not estimable because of 0 events in both arms.

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the optimal duration of adjuvant chemotherapy for colorectal cancer?

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the optimal duration of adjuvant chemotherapy for colorectal cancer?

Table 6: Economic evidence tables for the length of adjuvant treatment for colorectal cancer

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
Author & year: Robles-Zurita 2018 **Country:** United Kingdom **Type of economic analysis:** With-in Trial Cost Utility Analysis (CUA) **Source of funding:** The study was funded by the Medical Research	**Interventions in detail:** Intervention: 3 months of either oxaliplatin-containing adjuvant chemotherapy (CAPOX or FOLFOX). Comparator: 6 months of either oxaliplatin-containing adjuvant chemotherapy (CAPOX or FOLFOX). The choice of either CAPOX or FOLFOX was decided by the doctor and patient prior to randomisation.	**Population characteristics:** Patients with fully resected high-risk stage II or stage III colorectal cancer suitable for adjuvant therapy. The mean age of the cohort was 64 years old and was 67% male. **Modelling approach:** With-in trial economic evaluation **Source of base-line and effectiveness data:** All effectiveness data was taken from the SCOT trial (Iveson 2018) reported in detail in the clinical evidence review. **Source of cost data:**	**CAPOX** **Total cost 3 month regimen:** £17,650 **Total cost 6 month regimen** £21,503 **Total QALYs 3 month regimen:** 5.34 **Total QALYS 6 month regimen** 5.16 **Incremental Costs** -£3,853 **Incremental QALYS** 0.19	**Perspective:** Third-party payer perspective – UK NHS and Personal Social Services. **Currency:** UK pound sterling (£). **Cost year:** 2016 **Time horizon:** 3-8 years as per the SCOT trial **Discounting:** 3.5% per year for both costs and QALYs

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
Council and Cancer Research UK		Resource use was collected at the patient level. All treatment, follow-up and other medical costs were collected during the follow-up period of the trial. (3-8 years) Chemotherapy and other drugs were costed using the British National Formulary. Direct and non-direct hospitalisation costs were obtained from Information Services Division (ISD) of the National Health Service Scotland. **Source of QoL data:** A subsample of 1832 patients were given the EQ-5D-3L at baseline and all study follow-up appointments. The responses were scored using the UK general population tariffs.	**ICER** 3 month regimen dominant **FOLFOX** **Total cost 3 month regimen:** £19,641 **Total cost 6 month regimen** £26,483 **Total QALYs 3 month regimen:** 5.21 **Total QALYS 6 month regimen** 5.33 **Incremental Costs** -£6,841 **Incremental QALYS** -0.12 **ICER** £57,008 per QALY (as both incremental costs and incremental QALYs are nega-	**Applicability:** The study was deemed *directly applicable* to the decision problem. **Limitations:** The study was deemed to have only minor methodological limitations. The time horizon was potentially too short to capture all key cost and health differences between the groups and no attempt was made to model beyond the time horizon of the trial. There may particularly be large differences between the groups on the use of expensive palliative treatments. **Other comments:** The 'headline results reported in the study were for combined groups for FOLFOX and CAPOX. As the

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
			tive a higher QALY favours the intervention (3 month regimen) as it represents a cost saving per QALY forgone) **Probabilistic sensitivity analysis:** Probabilistic sensitivity analysis was conducted. At the NICE threshold of £30,000 per QALY, the 3 month regimen had a probability of being cost effective of 99.9% for CALPOX and 77.2% for FOLFOX. For £20,000 per QALY threshold (read from the reported CEACs) the probabilities were greater than 99.9% and 90% respectively.	committee found this combined analysis of limited use the disaggregated results reported in the supplementary material are presented here.

CAPOX: capecitabine and oxaliplatin CEAC: Cost Effectiveness Acceptability Curve; FOLFOX: folinic acid, fluorouracil and oxaliplatin ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year; QoL: quality of life

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the optimal duration of adjuvant chemotherapy for colorectal cancer?

Table 7: Economic evidence profiles for the length of adjuvant treatment for colorectal cancer

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Robles-Zurita 2018	Patients with fully resected high-risk stage II or stage III colorectal cancer suitable for adjuvant therapy.	CAPOX						Probabilistic sensitivity analysis was conducted. At the NICE threshold of £30,000 per QALY, the 3 month regimen had a probability of being cost effective of 99.9% for CALPOX and 77.2% for FOLFOX. For £20,000 per QALY threshold (read from the reported CEACs) the probabilities were greater than 99.9% and 90% respectively.	The study was deemed *directly applicable* to the decision problem. The study was deemed to have only minor methodological limitations. The time horizon was potentially too short to capture all key cost and health differences between the groups and no attempt was made to model beyond the time horizon of the trial. There may particularly be large differences between the groups on the use of expensive palliative treatments.
		6 month	£21,503	5.16 QALYs	Reference				
		3 month	£17,650	5.34 QALYs	-£3,853	0.19 QALYs	Dominant		
		FOLFOX							
		6 month	£26,483	5.33	Reference				
		3 month	£19,641	5.21 QALYs	-£6,841	-0.12 QALYs	£57,008 per QALY		

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
	Notes: The 'headline results reported in the study were for combined groups for FOLFOX and CAPOX. As the committee found this combined analysis of limited use the disaggregated results reported in the supplementary material are presented here.								

CAPOX: capecitabine and oxaliplatin CEAC: Cost Effectiveness Acceptability Curve; FOLFOX: folinic acid, fluorouracil and oxaliplatin ICER: incremental cost effectiveness ratio; Incr: Incremental QALY: quality adjusted life year; QoL: quality of life

Appendix J – Economic analysis

Economic analysis for review question: What is the optimal duration of adjuvant chemotherapy for colorectal cancer?

No economic analysis was conducted for this review question.

1 Appendix K – Excluded studies

2 Excluded clinical studies for review question: What is the optimal duration 3 of adjuvant chemotherapy for colorectal cancer?

4 **Table 8: Excluded studies and reasons for their exclusion**

Study	Reason for exclusion
Chau, I., Norman, A. R., Cunningham, D., Tait, D., Ross, P. J., Iveson, T., Hill, M., Hickish, T., Lofts, F., Jodrell, D., Webb, A., Oates, J. R. A randomised comparison between 6 months of bolus fluorouracil/leucovorin and 12 weeks of protracted venous infusion fluorouracil as adjuvant treatment in colorectal cancer. Ann Oncol, 549-557, 2005	Duplicate
Des Guetz, G., Uzzan, B., Morere, J. F., Perret, G., Nicolas, P., Duration of adjuvant chemotherapy for patients with non-metastatic colorectal cancer, Cochrane database of systematic reviews (Online), CD007046, 2010	Cochrane systematic review from 2010. None of the included studies are relevant for to this review because they compare longer durations
Haller, Dg, Catalano, Pj, Macdonald, Js, O'Rourke, Ma, Frontiera, Ms, Jackson, Dv, Mayer, Rj, Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089, Journal of clinical oncology, 23, 8671-8678, 2005	Intervention and comparison not according to review protocol
Hirata, K, Nakahara, S, Shimokobe, T, Imamura, T, Sakamoto, Y, Hirano, T, Abe, R, Kuroki, N, Konomi, K, Kato, H, Fujiwara, H, Fukuyama, N, Hotokezaka, M, Miyazaki, Y, Terasaka, R, Shiraishi, M, Miyazaki, R, Iwashita, A, Nakano, S, Ito, H, A randomized controlled trial of postoperative adjuvant chemotherapy for colorectal cancer-optimal duration of the treatment, Gan to kagaku ryoho. Cancer & chemotherapy, 36, 77-82, 2009	Full text in Japanese
Ito, K, Okushiba, S, Morikawa, T, Kondo, S, Katoh, H, Appropriate duration of postoperative oral adjuvant chemotherapy with HCFU for colorectal cancer, Gan to kagaku ryoho. Cancer & chemotherapy, 31, 55-59, 2004	Full text in Japanese
Ito, K., Kato, T., Koike, A., Miura, K., Yamaguchi, A., Sakou, T., Takagi, H., Optimum duration of oral adjuvant chemotherapy of HCFU for colorectal cancer; review of 5-year follow-up, Anticancer Research, 20, 4681-4686, 2000	This study compares adjuvant chemotherapy duration of 3 months to 18 months, not relevant according to the protocol
Iveson, T, Kerr, R, Saunders, Mp, Hollander, Nh, Tabernero, J, Haydon, Am, Glimelius, B, Harkin, A, Scudder, C, Boyd, K, Waterston, Am, Medley, Lc, Wilson, C, Ellis, R, Essapen, S, Dhadda, As, Harrison, M, Falk, S, Raouf, S, Paul, J, Final DFS results of the SCOT study: an International Phase III Randomised (1: 1) Noninferiority Trial comparing 3 versus 6 months of oxaliplatin based adjuvant chemotherapy for colorectal cancer, Journal of clinical oncology. Conference: 2017 annual meeting of the american society of clinical oncology, ASCO. United states, 35, 2017	Conference abstract
Iveson, T., Kerr, R., Saunders, M., Hollander, N., Tabernero, J., Haydon, A., Glimelius, B., Harkin, A., Scudder, C., Boyd, K., Waterston, A., Medley, L., Wilson, C., Ellis,	Conference abstract

Study	Reason for exclusion
R., Essapen, S., Dhadda, A., Harrison, M., Falk, S., Abdel-Raouf, S., Paul, J., Updated results of the SCOT study: An international phase III randomised (1:1) non-inferiority trial comparing 3 versus 6 months of oxaliplatin based adjuvant chemotherapy for colorectal cancer, Annals of Oncology, 28 (Supplement 5), v613, 2017	
Jonker, D. J., Spithoff, K., Maroun, J., Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based, Care, Adjuvant systemic chemotherapy for Stage II and III colon cancer after complete resection: an updated practice guideline, Clinical Oncology (Royal College of Radiologists)Clin Oncol (R Coll Radiol), 23, 314-22, 2011	A practice guideline and systematic review. No relevant comparisons
Nakamura, T., Ohno, M., Tabuchi, Y., Kamigaki, T., Fujii, H., Yamagishi, H., Kuroda, Y., Kansai Carmofur Study, Group, Optimal duration of oral adjuvant chemotherapy with Carmofur in the colorectal cancer patients: the Kansai Carmofur Study Group trial III, International Journal of Oncology, 19, 291-8, 2001	This study compares adjuvant chemotherapy duration of 6 months to 12 months, not relevant according to the protocol
Neugut, A. I., Matasar, M., Wang, X., McBride, R., Jacobson, J. S., Tsai, W. Y., Grann, V. R., Hershman, D. L., Duration of adjuvant chemotherapy for colon cancer and survival among the elderly, Journal of Clinical Oncology, 24, 2368-75, 2006	Observational study
Sadahiro, S, Tsuchiya, T, Sasaki, K, Kondo, K, Katsumata, K, Nishimura, G, Kakeji, Y, Baba, H, Sato, S, Koda, K, Yamaguchi, Y, Morita, T, Matsuoka, J, Usuki, H, Hamada, C, Kodaira, S, Randomized phase III trial of treatment duration for oral uracil and tegafur plus leucovorin as adjuvant chemotherapy for patients with stage IIB/III colon cancer: final results of JFMC33-0502, Annals of oncology : official journal of the european society for medical oncology, 26, 2274-2280, 2015	This study compares adjuvant chemotherapy duration of 6 months to 18 months, not relevant according to the protocol
Sobrero, A., Lonardi, S., Rosati, G., Di Bartolomeo, M., Ronzoni, M., Pella, N., Scartozzi, M., Banzi, M., Zampino, M. G., Pasini, F., Marchetti, P., Cantore, M., Zaniboni, A., Rimassa, L., Ciuffreda, L., Ferrari, D., Zagonel, V., Maiello, E., Barni, S., Rulli, E., Labianca, R., Tosca Investigators, FOLFOX or CAPOX in Stage II to III Colon Cancer: Efficacy Results of the Italian Three or Six Colon Adjuvant Trial, J Clin Oncol, 36, 1478-1485, 2018	This trial (TOSCA trial, part of the IDEA collaboration) has been included in the review but this publication does not report any additional outcomes (see Lonardi 2016 and Grothey 2018)
Suto, T., Ishiguro, M., Hamada, C., Kunieda, K., Masuko, H., Kondo, K., Ishida, H., Nishimura, G., Sasaki, K., Morita, T., Hazama, S., Maeda, K., Mishima, H., Ike, H., Sadahiro, S., Sugihara, K., Okajima, M., Saji, S., Sakamoto, J., Tomita, N., Preplanned safety analysis of the JFMC37-0801 trial: a randomized phase III study of six months versus twelve months of capecitabine as adjuvant chemotherapy for stage III colon cancer.[Erratum appears in Int J Clin Oncol. 2017 Aug;22(4):805-806; PMID: 28608229], International Journal of Clinical Oncology, 22, 494-504, 2017	This study compares adjuvant chemotherapy duration of 6 months to 12 months, not relevant according to the protocol
Tsuchiya, T., Sadahiro, S., Sasaki, K., Kondo, K., Katsumata, K., Nishimura, G., Kakeji, Y., Baba, H., Morita, T., Koda, K., Sato, S., Matsuoka, J., Yamaguchi, Y., Usuki, H., Hamada, C., Kodaira, S., Saji, S., Safety analysis of	This study compares adjuvant chemotherapy duration of 6 months to 18 months, not relevant according to the protocol

Study	Reason for exclusion
two different regimens of uracil-tegafur plus leucovorin as adjuvant chemotherapy for high-risk stage II and III colon cancer in a phase III trial comparing 6 with 18 months of treatment: JFMC33-0502 trial, Cancer Chemotherapy & PharmacologyCancer Chemother Pharmacol, 73, 1253-61, 2014	
You, K. Y., Huang, R., Yu, X., Liu, Y. M., Gao, Y. H., Is it possible to shorten the duration of adjuvant chemotherapy for locally advanced rectal cancer? Medicine (United States), 95 (16) (no pagination), 2016	Wrong study design, this is a retrospective observational study

1

Appendix L – Research recommendations

Research recommendations for review question: What is the optimal duration of adjuvant chemotherapy for colorectal cancer?

No research recommendations were made for this review question.