**Table 1: NHMRC Evidence Statement for clinical question: ADJ1**

<table>
<thead>
<tr>
<th>PICO Question ADJ1:</th>
<th>Report body of evidence tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>In elderly patients (≥70 years) diagnosed with colon cancer, what is the efficacy of surgery and adjuvant combination chemotherapy (involving either 5-fluorouracil or capecitabine combined with oxaliplatin), compared to surgery with a single chemotherapeutic agent (Fluoropyrimidine), in achieving the best outcomes in terms of colorectal cancer mortality, recurrence, quality of life and adverse effects?</td>
<td></td>
</tr>
</tbody>
</table>

**1. Evidence base** *(number of studies (quantity), level of evidence and risk of bias in the included studies – see body of evidence tables in report)*

| A | One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias |
| B | One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias |
| C | One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias |
| D | Level IV studies or Level I to III studies/SRs with a high risk of bias |

Eight Level II studies compared the efficacy of oxaliplatin-based chemotherapy combinations to the single chemotherapy FULV (5-flourouracil and leucovorin) in elderly patients who had undergone surgery. All studies were at risk or unclear risk of bias due to the open-label nature of their designs.

These studies covered three large randomised control trials: MOSAIC (Multicentre International Study of Oxaliplatin/5-fluorouracil/leucovorin in the Adjuvant Treatment of Colon Cancer), XELOXA (XELOX in adjuvant colon cancer treatment) and NSABP C-07 (National Surgical Adjuvant Breast and Bowel Project Protocol C-07). A total of 1,023 patients were greater than 70 years of age and analysed across these trials. Patients from MOSAIC and NSABP-C07 underwent resection of stage II or III colon cancer and those from XELOXA underwent curative surgery for stage III colon cancer.

Primary outcome reported across the trials was disease free survival. Overall survival was reported by all three trials as a secondary outcome. MOSAIC and NSABP C-07 further reported adverse events, toxicity and safety as additional secondary outcomes.

The XELOXA trial ran from 2003 to 2004 with a final median follow up of 7 years. The intervention arm received XELOX (130mg/m² of oxaliplatin with 1000mg/m² of capecitabine) while the comparator group received FULV according to the Mayo Clinic or Roswell Park regime (5-fluorouracil at 425mg/m² or 500mg/m² with leucovorin at 20mg/m² or 500mg/m²). A total of 409 patients were ≥70 years of age at randomisation.

The MOSAIC trial ran from 1998 to 2001 with a final median follow up of 9.5 years. The intervention arm received FOLFOX4 (an FULV regimen with 85mg/m² of oxaliplatin) while the comparator group received FULV (200mg/m² of leucovorin with 400mg/m² 5-fluorouracil). A total of 315 patients were ≥70 years of age and randomisation.
The NSABP C-07 trial ran from 2000 to 2002 with a final median follow up of 8 years calculated by reverse censoring. The intervention arm received FLOX (FULV Roswell Park regime with 85mg/m² of oxaliplatin) while the comparator group received the Roswell Park regime of FULV (500mg/m² of leucovorin with 500mg/m² of 5-fluorouracil). A total of 299 patients were ≥70 years of age at randomisation.

One Level I study (McCleary et al. 2013) pooled data from trials that compared oxaliplatin-based combination chemotherapy to FULV in elderly patients with a range of 36 to 74 months in median follow up. The primary outcomes studied in this analyses was disease free survival. Overall survival was a secondary outcome. Additional secondary outcomes were recurrence and mortality. This meta-analysis was of high risk of bias as their choice of studies appeared arbitrary and did not provide a protocol as to how the studies were chosen. McCleary et al. (2013) pooled data from MOSAIC, NSABP C-07 and XELOXA. The study characteristics of these trials have been described above. McCleary et al. (2013) reports a patient population of 1,119 who are of or greater than 70 years of age.

### Grade D

#### 2. Consistency

If only one study was available, rank this component as ‘not applicable’

<table>
<thead>
<tr>
<th>Disease free Survival</th>
<th>A</th>
<th>All studies consistent</th>
</tr>
</thead>
</table>
| Adjuvant combination chemotherapy did not appear to be any more significantly effective than single chemotherapy in elderly patients in the NSABP C-07 trial (HR=1.03, 95% CI 0.77 – 1.36, p=0.87). Those who received combination chemotherapy reported 62.8% DFS whereas those who received single chemotherapy reported 62% (Yothers, et al. 2011). This was the same in MOSAIC where Tournigand et al. 2012 did not report a significant improvement in DFS (p=0.71). Although elderly patients in the FOLFOX group reported 69.1% DFS at 5 years in comparison to those with single chemotherapy at 65.8% (HR=0.93 with 95% CI 0.64 – 1.35).
| B | Most studies consistent and inconsistency can be explained |
| C | Some inconsistency, reflecting genuine uncertainty around question |
| D | Evidence is inconsistent |
| NA | Not applicable (one study only) |

Specific endpoints and significance were not reported for DFS in XELOXA. However, HR=0.75 (95% CI 0.6-1.0) in patients older than 65 years which did not suggest a strong benefit to combination chemotherapy. After median follow up of 74 months, the benefit continued to slip for the efficacy of combination chemotherapy (Schmoll et al. 2015) with HR=0.86 (0.65 – 1.16).

While McCleary et al. 2013 did not report this endpoint, the pooled analysis further...
supports that there is weak evidence (p=0.09) for the efficacy of combination over single chemotherapy at HR=0.94 (95% CI 0.78 – 1.13) for DFS. Combination chemotherapy appears to provide no significant benefit over a single chemotherapy regime in terms of DFS in elderly patients.

**Grade A**

**Overall Survival**
Adjuvant combination chemotherapy had poor evidence for a benefit in overall survival for elderly patients in NSABP C-07 with p=0.3 (Yothers et al. 2011). After a median follow up of 8 years, patients who underwent combination chemotherapy reported 71.6% while those who received single chemotherapy regimens showed slightly higher rates of overall survival at 76.3%. Single chemotherapy regimens was observed to show improved overall survival with HR=1.18 (95% CI 0.68 – 1.62).

This was also true of the MOSAIC trial where little strength was found to the evidence of an advantage given by combination chemotherapy. No significance was found by Tournigand et al. (2012) for 6 year overall survival with HR=1.10 (95% CI 0.73 – 1.65). Again after median follow up of 9.46 years, Andre et al. (2015) did not find a distinct benefit given by combination chemotherapy (p=0.338) with HR=1.19 (95% CI 0.83 – 1.7).

Strong evidence was reported for the efficacy of single chemotherapy than combination chemotherapy (p=0.033) where HR=1.52 (95% CI 1.04 – 2.49). FOLFOX patients reported 3.6 months for the median overall survival in contrast to FULV patients who reported 13.7 months after a median follow up of 80 months. The XELOXA trial similarly showed a weak benefit given by combination chemotherapy where HR=0.91 (95% CI 0.66 – 1.26) although the significance and endpoints of overall survival was not reported.

In pooling data from these trials reported by McCleary 2013, adjuvant combination chemotherapy did not confer a particular benefit over single chemotherapy regimens in elderly patients with HR=1.04 (95% CI 0.85 – 1.27). Overall, studies appear to agree that combination chemotherapy provided little to no significant advantage over single chemotherapies in elderly patients for overall survival.

**Grade A**

**Adverse events**
Both NSABP C-07 and MOSAIC found higher rates of adverse events in patients who
received adjuvant combination chemotherapy. There was particularly strong evidence for this by Kuebler et al. (2007) where 6.8% of patients from NSABP C-07 who underwent combination chemotherapy reported a bowel wall injury in contrast to 2.7% of those who received a single chemotherapy regime (p<0.01). After a median follow up of 8 years, Yothers et al. (2011) reported an OR of 1.59 (95% CI 0.93 – 2.73) which provide further evidence that single chemotherapies were associated with less toxicity. Toxicity was reported in 13% of single chemotherapy patients while 19.3% was reported for combination chemotherapy patients. Tournigand et al. (2012) reported significantly greater rates of severe adverse events with combination chemotherapy treatment at 19.4% compared to 9.4% in single chemotherapy patients (p=0.018) during MOSAIC.

This trend was repeated among other particular adverse events in a subgroup analysis of NSABP C-07 however significance of these are not known as this and size of effects were not reported.

**Grade A**

### Recurrence

Adjuvant combination chemotherapy provided little benefit over single chemotherapy in MOSAIC. For patients older than 65 years, HR was 0.96 (95% CI 0.72 – 1.24) (Andre et al 2004). At 5 year time to recurrence, Tournigand et al. (2012) reported poor significance to a small benefit given to patients older than 70 years by combination chemotherapies (p=0.14). Although the endpoints were not reported, HR was 0.72 (95% CI 0.47-1.11).

More recurrence was reported in combination chemotherapy patients after median follow up of 63 months. FOLFOX patients were reported at 24% and FULV patients reported 18%. Interestingly, in a subgroup analysis of relapse (those requiring further surgery to manage metastases), significantly fewer combination chemotherapy patients were reported, 5.8% in contrast to 13.8% of single chemotherapy patients (p=0.01).

McCleary et al (2013) pooled analyses also found very poor significance (p=0.36) to the little benefit given by combination chemotherapy in terms of recurrence in elderly patients (HR=0.86, 95% CI 0.69 – 1.06).

Adjuvant combination chemotherapy showed little to no benefit over single chemotherapy regimens in elderly patients. There was poor evidence to suggest any advantage given
by combination chemotherapies.  

**Grade A**

**Mortality and Deaths**  
For patients in MOSAIC older than 65 years, HR was reported at 1.0 for mortality (95% CI 0.76 – 1.32) (Andre et al. 2009). After a median follow up of up to 80 months, Tournigand et al. (2012) reported marginally smaller deaths for those greater than 70 years of age. In combination chemotherapy patients, 20% was observed compared to 22% in single chemotherapy patients. Significance and size of effect was not reported.

After pooling data, McCleary et al. (2013) reported higher deaths with 3.15% in combination chemotherapy patients and 2.25% in single chemotherapy patients. This had very poor significance where p=0.4.

There is mixed evidence with poor or unknown significance to determine any benefit given by combination chemotherapy for the mortality of elderly patients.  

**Grade A**

### 3. Clinical impact
See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)

<table>
<thead>
<tr>
<th>Disease free Survival</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very large</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Substantial</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Slight/Restricted</strong></td>
<td></td>
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</tbody>
</table>

There was very poor to no significance found to any advantages given by adjuvant combination chemotherapy for DFS. XELOXA did not report the significance of their findings but both MOSAIC and NSABP C-08 reported particularly weak significance (p=0.71 and p=0.87 respectively). The poor significance behind any evidence for an advantage given by combination chemotherapy remained after McCleary et al. (2013) pooled data (p=0.09). Adjuvant combination chemotherapy provided little to no benefit over single chemotherapy for the DFS of elderly patients and showed no statistical significance for any benefit.  

**Grade D**
Overall Survival
Schmoll et al. (2015) did not report the significance of their findings in XELOXA although there seemed weak significance to any advantage potentially conferred by adjuvant combination chemotherapy (HR=0.91, 95% CI 0.66 – 1.26).

In MOSAIC, Tournigand et al. (2012) reported a statistically significant shorter median overall survival for those that received combination chemotherapies (p=0.033), 3.6 months to 13.7 months in those who were treated with single chemotherapies (HR=1.52, 95% CI 1.04 – 2.49). Of the remaining studies in MOSAIC, no significance was found for any observed benefits for overall survival due to adjuvant combination chemotherapy (p=0.661 for 6 year overall survival, p=0.338 at 9.46 years of median follow up). At 6 year overall survival, there was no particular advantage over single chemotherapies (HR=1.10, 95% CI 0.73 – 1.65) and after 9.46 years of median follow up (HR=1.19, 95% CI 0.83 – 1.7). Likewise, Yothers et al. (2011) reported no statistical difference between the two treatments (p=0.3).

In a pooled analyses, McCleary et al. (2013) reported weak evidence to suggest an advantage given by adjuvant combination chemotherapy with an HR of 1.04 (95% CI 0.85 – 1.27, p=0.05)

Overall, there is little evidence to suggest that adjuvant combination chemotherapy improves overall survival in elderly patients.

Grade D

Adverse events
In NSABP C-07, Kuebler et al. (2007) reported strong significance to greater rates of bowel wall injuries in patients older than 65 years who received combination chemotherapies (p<0.01). 6.8% of combination chemotherapy patients older than 70 years of age was reported in comparison to 2.7% in single chemotherapy patients. After 8 years median follow up, this was further confirmed (OR=1.59, 95% CI 0.93 – 2.73) where 19.3% of combination chemotherapy patients reported incidences of Grade 4 to 5 toxicity in contrast to 13% of single chemotherapy patients.

In MOSAIC, patients older than 70 years of age reported statistically significant severe adverse events in 19.4% of combination chemotherapy patients in comparison to 9.4%
of single chemotherapy patients (p=0.018).

No further significance or size of effect was reported for the remaining outcomes associated with adverse events. However, there was a consistent trend of higher rates for these adverse events in elderly patients who underwent combination chemotherapy.

Grade B

Recurrence
At median follow up of 37.9 months, there appeared weak significance to any benefit given by combination chemotherapy in terms of recurrence in patients older than 65 years of age (HR=0.96, 95% CI 0.72 - 1.24) as part of the MOSAIC trial (Andre 2004). However, after median follow up of 63 months, Tournigand et al. (2012) reported a higher rate of overall recurrence in patients older than 70 years of age who received combination chemotherapy relative to single chemotherapy patients. This was reported at 24% and 18% respectively. The significance and size of effect of this was not reported.

At 5 year time to recurrence, this lost its significance (p=0.14, HR=0.72, 95% CI 0.47 – 1.11). McCleary et al.'s (2013) pooled analyses found no statistical significance (p=0.36) to any advantage given by combination chemotherapy for time to recurrence in elderly patients (HR=0.86, 95% CI 0.69 – 1.06)

There has generally been no statistical significance found for the studies that have shown minimal benefit for recurrence in patients who received combination chemotherapy.

Grade D

Mortality/Deaths
At the end of 81.9 months of median follow up in MOSAIC, Andre et al. (2009) reported little difference in terms of mortality between the two treatment arms in patients older than 65 years of age (HR=1.0, 95% CI 0.76 – 1.32). This was reflected in patients older than 70 years of age. Deaths were reported relatively fewer in 20% of combination chemotherapy patients and 22% in single chemotherapy patients. Significance or size of effect of this was not reported.

McCleary et al. (2013) similarly found no statistical significance between the two groups
Although combination chemotherapy patients reported slightly higher mortality rates at 3.15% in contrast to 2.25% of single chemotherapy patients.

**Grade D**

### 4. Generalisability
*(How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)*

For study population characteristics see table of study characteristics in report

NSABP C-07 ran in New Zealand and in the USA. MOSAIC and XELOXA were conducted over several developed countries including Australia. It is likely that the evidence can be directly generalised to local clinical settings. All drug regimens used in these trials are also in common use among the colon surgical context in Australia.

All patients included across the trials were of either stage II or III colon cancer, the majority being of stage III. However, it is not clear the proportion of this across elderly patients older than 70 years of age. All patients had also undergone resection of their cancer and were free of complications before adjuvant chemotherapy. For studies that were included in the analyses, all patients were equal to or older than 70 years of age.

**Grade B**

### 5. Applicability
*(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

Adjuvant combination chemotherapy is standard treatment for patients with stage III colon cancer in Australia and would be readily available to elderly patients if need be. The gap lies in patterns of care within hospitals. Clinicians have been known to provide treatment to older patients at sub optimal doses (Wong, 2013 [http://jco.ascopubs.org/content/31/4/511.2.full](http://jco.ascopubs.org/content/31/4/511.2.full)) and in a 2008 Australian survey, more than 90% of the clinicians reported lower than standard dosing for a fit 75-year old patient (Field KM, Kosmider S, Jefford M, et al. (2008) Chemotherapy dosing strategies in the obese, elderly, and thin patient: Results of a nationwide survey. J Oncol Pract 4:108–113.). Practices also differ between oncologists and surgeons and may be influenced by the hospital practices where the surgery is performed.

**Grade B**

Current evidence may be surprising in suggesting there is little difference between adjuvant combination chemotherapy and single chemotherapy at standard doses for elderly patients.

Capecitabine and oxaliplatin are subsidised drugs by the Pharmaceutical Benefits Scheme for adjuvant treatment of stage III colon cancer and can be reimbursed as part of a combination chemotherapy regime. This may become a caveat in terms of costs for elderly patients with stage II colon cancer. Fluorouracil is also subsidised at any stage (Bowel Cancer Aus.org/chemotherapy). Drug regimens used for adjuvant combination chemotherapy are generally affordable within the Australian health care context.

Currently, those aged over 70 years for chemotherapy are less likely to receive combination chemotherapy treatment and the evidence found aligns with this trend.

**Grade A**

<table>
<thead>
<tr>
<th>Other factors</th>
<th>(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).)</th>
</tr>
</thead>
</table>


The studies included did not report on quality of life. Significance and size of effects were often not reported which make it difficult to determine the true impact of the treatment on many outcomes. These trials purely looked at fit older patients. Risk factors such as microsatellite instability has been noted in older patients and has been associated with reduced or no benefit from adjuvant chemotherapy (Sargent DJ, Marsoni S, Monges G, et al. (2010) Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol 28:3219–3226.).

**EVIDENCE STATEMENT MATRIX**

_Please summarise the development group’s synthesis of the evidence relating to the key question, taking all the above factors into account._

<table>
<thead>
<tr>
<th>Component</th>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evidence base</td>
<td>D</td>
<td>Three RCTS (Level II studies) at high risk of bias. One Level I study at high risk of bias.</td>
</tr>
<tr>
<td>2. Consistency</td>
<td>A</td>
<td>Grade A - Disease Free Survival</td>
</tr>
<tr>
<td>2. Consistency</td>
<td>A</td>
<td>Grade A - Overall Survival</td>
</tr>
<tr>
<td>2. Consistency</td>
<td>A</td>
<td>Grade A - Adverse Events</td>
</tr>
<tr>
<td>2. Consistency</td>
<td>A</td>
<td>Grade A - Recurrence</td>
</tr>
<tr>
<td>2. Consistency</td>
<td>A</td>
<td>Grade A - Mortality and Deaths</td>
</tr>
<tr>
<td>3. Clinical impact</td>
<td>D</td>
<td>Grade D - Disease Free Survival</td>
</tr>
<tr>
<td>3. Clinical impact</td>
<td>D</td>
<td>Grade D - Overall Survival</td>
</tr>
<tr>
<td>3. Clinical impact</td>
<td>B</td>
<td>Grade B - Adverse Events</td>
</tr>
<tr>
<td>3. Clinical impact</td>
<td>D</td>
<td>Grade D - Recurrence</td>
</tr>
<tr>
<td>3. Clinical impact</td>
<td>D</td>
<td>Grade D - Mortality and Deaths</td>
</tr>
<tr>
<td>4. Generalisability</td>
<td>B</td>
<td>Evidence directly generalisable to target population with some caveats</td>
</tr>
<tr>
<td>5. Applicability</td>
<td>A</td>
<td>Evidence directly applicable to Australian healthcare context</td>
</tr>
</tbody>
</table>
Evidence statement:
In elderly patients (≥ 70 years) following surgery for stage III colon cancer, subset analyses of three randomised controlled trials found no survival benefit from the addition of oxaliplatin to a fluoropyrimidine containing adjuvant chemotherapy (involving either 5-fluorouracil or capecitabine), compared to adjuvant chemotherapy with a fluoropyrimidine alone.

RECOMMENDATION
What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.

No evidence-based recommendations were made.

PRACTICE POINT OR CONSENSUS-BASED RECOMMENDATION
If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation or practice point can be given.

Consensus-based recommendation:
Elderly patients (≥ 70 years) with stage III colon cancer who are fit for adjuvant chemotherapy should receive 6 months of a single-agent fluoropyrimidine (either 5FU or capecitabine).

Practice points:
- The addition of oxaliplatin to adjuvant fluoropyrimidine-based therapy in elderly patients (≥70 years) with stage III colon cancer did not improve survival outcomes.
Table 2: Unresolved issues

UNRESOLVED ISSUES
If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.

While oxaliplatin-based treatment provides a similar advantage for older and younger patients with metastatic disease, the data do not support this approach in older patients in the adjuvant setting. Therefore, oxaliplatin-based therapy cannot be recommended for older patients.

Table 3: Implementation of recommendation

IMPLEMENTATION OF RECOMMENDATION
Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.

Will this recommendation result in changes in usual care? NO
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there any resource implications associated with implementing this recommendation?</td>
<td>NO</td>
</tr>
<tr>
<td>Will the implementation of this recommendation require changes in the way care is currently organised?</td>
<td>NO</td>
</tr>
<tr>
<td>Are the guideline development group aware of any barriers to the implementation of this recommendation?</td>
<td>NO</td>
</tr>
</tbody>
</table>