NHRMC Evidence Statement Forms

Table 1: NHMRC Evidence Statement for clinical question: PPR1

What is the risk-benefit ratio for use of aspirin for prevention of colorectal cancer stratified by risk of colorectal cancer itself? (What is the optimal dose and frequency of administration?)

PICO Question PPR1: In an asymptomatic population at average risk or increased risk of colorectal cancer, what is the cost-benefit ratio of prophylactic Aspirin use in reducing the mortality and incidence of colorectal cancer?	**Report body of evidence tables**	
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)*		
Average Risk Population Five Level II studies reported randomised controlled trials comparing aspirin use with placebo or no aspirin use. Four Level II studies (SALT, UK-TIA, WHS, TPT) were at low risk of bias, and the British Doctors Aspirin Trial (Peto *et al.,* 1988) was at risk of bias, as the study design was not blinded (no placebo pill used). Frequency of aspirin use was either daily for most trials, except the WHS trial which was alternating days. The aspirin dosage varied from 75mg/day (TPT, SALT) or 100mg on alternating days (WHS) to 1200mg/day (UK-TIA). Study outcomes reported included colorectal cancer incidence and mortality, gastrointestinal side effects, as well and other cancer incidence, cancer mortality, and fatal or non-fatal cardiovascular events. Follow-up for most trials was approximately 20 years. The number of participants in the trials varied from 1360 (SALT) to nearly 40,000 in the WHS trial. Three trials (SALT, UK-TIA, TPT) recruited participants with a transient ischemic attack or minor ischaemic stroke or were at high risk of ischaemic heart disease. In contrast, the WHS and BDAT trials recruited healthy healthcare professionals (female or male, respectively). A limitation to these trials is that none of them had colorectal cancer as the primary endpoint, and none were colonoscopically controlled. Most studies did not report on aspirin exposure after the randomised interventional period. The WHS trial did have cancer as a primary endpoint (any invasive cancer, excluding non-melanoma skin cancer), but the incidence of colorectal cancer was a secondary endpoint. **Grade B** **High Risk Population**	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**

Five Level II studies reported on randomised controlled trials comparing daily aspirin to placebo. Two trials (AFPPS and APACC) compared lower-dose aspirin (defined as 81mg or 160 mg/day) and higher-dose aspirin (defined as 300mg or 325 mg/day) to placebo. The remaining trials (CALGB, CAPP2 and ukCAP) compared higher-dose aspirin to placebo (325mg, 600mg, or 300mg/day, respectively). All studies were at low risk of bias. In the CAPP2 trial, eligible participants (N=671) were >25 years of age and were proven carriers of a pathologic mismatch-repair mutation or members of a family that met the Amsterdam diagnostic criteria and had a personal history of a cured Lynch syndrome neoplasm but an intact colon. Colonoscopic examination and clearance of polyps within 3 months after recruitment were prerequisites to study entry. Study primary outcomes included the detection of at least one adenoma or colorectal carcinoma at follow up. In the AFPPS, APACC, and ukCAP trials, participants were recruited who had a recent history of sporadic colorectal adenomas and excluded individuals with a history of invasive large-bowel cancer. The CALGB trial specifically recruited patients who had been treated for colorectal cancer. Other eligibility criteria for these four trials were similar, with each trial excluded individuals with inflammatory bowel disease, those with a clinical need for aspirin treatment, and those who could not take aspirin. All four trials (AFPPS, APACC, CALGB, and ukCAP) used adenoma incidence as a primary endpoint. The CAPP2 trial had a mean follow-up was 5.5 years, and the other four trials had a median follow-up between 31.3 and 47.2 months.
Grade A

2. Consistency *(if only one study was available, rank this component as 'not applicable')* See body of evidence tables in report – results and p value (95% CI)		
Colorectal Cancer Incidence	A	**All studies consistent**
Average Risk Population	B	**Most studies consistent and inconsistency can be explained**
Three trials reported individual data for colorectal cancer incidence in average risk populations (WHS, BDAT, UK-TIA). The BDAT trial showed a statistically significant reduction in colorectal cancer incidence in whose taking 300mg/day aspirin, with 23 years of follow-up (HR=0.07, p=0.04). The WHS trial found a significant reduction in colorectal cancer incidence only after 16 years follow-up (HR=0.80, p=0.021), and not after 10 years follow-up (RR=0.97). This trial was not colonoscopically controlled, and its pre-defined primary endpoints were cardiovascular events or invasive cancer. In pooled data from the BDAT and UK-TIA trials with up to 23 years follow-up (Flossman *et al.*, 2007) aspirin use (BDAT used 300 or 500mg/day, UK-TIA used 300 or 1200mg/day)	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**

demonstrated a reduction in colorectal cancer incidence (HR=0.74, p=0.02). This reduction was not seen in the first 10 years after intervention (HR=0.92, CI=0.56-1.49). In non-pooled data from the UK-TIA or BDAT trials individually, both showed a reduction in colorectal cancer incidence only after 10 years of follow up (HR=0.50, p=0.05 and HR=0.64, p=0.05, respectively). Pooled analysis from Rothwell *et al.,* 2010 which included data from the BDAT, SALT, TPT and UK-TIA trials also showed a significant reduction in colorectal cancer incidence in those taking aspirin during the trial period and followed for a median of 18.3 years (HR=0.75 p=0.02). Subgroup analysis of this pooled data also showed that 2.5-5 years of aspirin consumption was just as beneficial as ≥5 years aspirin consumption (HR=0.69 and 0.62 respectively, p=0.003 for both). In addition, subgroup analysis of the pooled trial data on the location of cancer showed that aspirin was beneficial for proximal colon cancer (HR=0.45, p=0.001), but not for distal colon (HR=1.10 p=0.66) or rectal cancer (HR=0.90, p=0.58), with a median of 18.3 years follow-up. In modelling data reported by van Kruijsdijk 2015 on the WHS trial, aspirin was shown to be associated with a modest decreased 15-year risk of colorectal cancer, and the highest net benefit was only seen in the 10-year risk of colorectal cancer in women ≥65 years of age (NNT = 369).
Grade B

High Risk Population
For the CAPP2 trial in a high-risk population, no benefit in colorectal cancer incidence was report after 29.1 months or 66.1 month mean follow up (RR=1.0, HR=0.63/p=0.12, respectively) using intention-to-treat analysis. The most convincing benefit was found with per-protocol analysis, where aspirin reduced colorectal cancer incidence after ≥2 years on trial treatment (HR=0.41, p=0.02) compared to placebo with a mean of 66.1 months follow up. All Lynch Syndrome associated cancers provided the strongest outcome benefit. Both intention-to-treat and per-protocol analysis reported significant benefit after ≥2 years on trial treatment compared to placebo (HR=0.65, p=0.05 and HR=0.45, p=0.005 respectively). Note that there was no effect on adenomas suggesting that the effect was on the progression of adenomas to cancers.

The AFPPS, APACC, CALGB, and ukCAP trials only report incidence of adenoma and advanced lesions. In pooled meta-analysis of these trials, aspirin was shown to significantly reduce the risk of adenoma comparing any

dose of aspirin to placebo (RR=0.83, p=0.012). A reduction in advanced lesion risk was also reported then comparing any dose of aspirin to placebo (RR=0.72, p=0.0046) in pooled meta-analysis. In the individual trials, a reduction in adenoma incidence for any dose aspirin was reported for CALGB (RR=0.61, CI=0.44-0.86) and ukCAP (RR=0.79, CI=0.63-0.99) trials only, but not for the AFPPS (RR=0.88, p>0.05) or APACC (RR=0.95, p>0.05) trials. In the individual trials, only a significant reduction in risk was reported in the ukCAP trial (RR=0.63, CI=0.43-0.91) for advanced lesions comparing any dose of aspirin to placebo.

A significant reduction in the risk of adenoma (RR=0.83, p=0.012) was also reported in pooled meta-analysis comparing only low-dose aspirin (81mg or 160mg/day) to placebo (AFPPS and APACC trials). No risk reduction was reported in pooled data comparing only low-dose aspirin (81mg or 160mg/day) to placebo for advanced lesion (RR=0.83, p=0.57). As individual trials, significant risk reduction was only reported for the AFPPS trial (RR=0.81, CI=0.69-0.96).

A significant risk reduction was reported for advanced lesions when comparing higher dose aspirin (300mg or 325mg/day) to placebo in pooled meta-analysis (RR=0.71, p=0.0089), but no such difference was found for adenoma (RR=0.85, p=0.099).

In pooled analysis (Cole *et al.*, 2009) colorectal cancer incidence was reported as an adverse event, with participants taking aspirin (any dose), 9 cases (0.54%, N=1678) were diagnosed with colorectal cancer, compared to 8 cases (0.62%, N=1289) diagnosed in the placebo group (p=0.81).
Grade B

Colorectal Cancer Mortality
Low risk population
Of the 4 trials that reported individual trial data for mortality due to colorectal cancer (BDAT, SALT, TPT, UK-TIA), only the TPT trial reported a significant benefit (reduction) in colorectal cancer mortality for those taking aspirin with 17-20 years of follow-up (OR=0.73, CI=0.49-1.10). In meta-analysis by Rothwell *et al.,* 2010 of the BDAT, SALT, TPT, and UK-TIA trials, aspirin was found to be beneficial with a median of 18.3 years follow-up (OR=0.66, p=0.002). Subgroup analysis reported that this benefit was only for those who

took 300mg or less per day during the trial period. The benefit from aspirin consumption was seen irrespective of aspirin consumption duration (HR=0.54/p=0.001 for ≥2.5 years on trial and HR=0.48/p=0.001 for ≥5 years on trial)(Rothwell *et al.,* 2010). In addition, subgroup analysis of this meta-analysis on the location of colorectal cancer showed that aspirin was beneficial for proximal colon cancer (HR=0.34, p=0.001), but not for distal colon (HR=1.21, p=0.54) or rectal cancer (HR=0.80, p=0.35), with a median 18.3 year follow-up.

In subgroup meta-analysis of these 4 trials, reduction in colorectal cancer mortality as statistically significantly reduced in proximal colon cancer (HR=0.34, p=0.001), for participants taking aspirin vs placebo, compared to distal colon (p=0.54) or rectal cancer (p=0.35). The benefit for proximal cancer is particularly important given the concern that colonoscopic screening in many studies has not been shown to be protective against proximal colorectal cancer (thought to be due to poor bowel preparations, incomplete examinations, flat (sessile serrated) polyps easily overlooked and difficulty completely removing these polyps).
Grade B

High risk population
All 5 trials did not report colorectal cancer mortality data.
Grade N/A

Adverse Effects
Low risk population
Two trials (WHS, UK-TIA) reported adverse effects from aspirin consumption. In the WHS trial, those taking aspirin significantly experienced greater gastrointestinal bleeding and peptic ulcers (HR=1.14 and HR=1.17 respectively, p<0.001) compared to the placebo group. No difference was found for colon polyps between treatment groups (HR=1.00) though the trial was not colonoscopically controlled. Those taking 300mg/day aspirin in the UK-TIA also experienced significant greater gastrointestinal haemorrhage compared to the placebo (OR=1.32, CI=1.06-1.65) group (and also the 1200mg/day group (OR=1.54, CI=1.25-1.89), but not significant more than the 300mg/day group). The aspirin group in the WHS trial also experienced greater peptic ulcer events than the placebo group (HR=1.17, p<0.001). Participates taking aspirin in the UK-TIA trial also experienced significantly

greater upper gastrointestinal symptoms (OR=1.32, p<0.05), and more so with a higher aspirin dose of 1200mg/day (OR=1.54, p<0.05 compared to 300mg/day group). All of these trials document the adverse effects well during intervention but less well during the long periods of follow up that were needed to define the cancer incidence and mortality rates. However, aspirin side effects related to long term use in other large population studies is well documented and there is little reason to consider that dose equivalent side effects would be different for the participants in the trials considered here. Aspirin is off patent now and there is little interest in pursuing this question of long term side effects by industry at present.
Grade A

High risk population
The CAPP2 trial did not report statistical analysis of serious adverse events. In pooled analysis of the AFPPS, APACC, CALGB, and ukCAP trials, the only adverse event that reported a significant reduction in participants on aspirin compared to placebo was stroke (p=0.002).
Grade N/A

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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)*

Low risk population	A	**Very large**
A significant benefit in reducing colorectal cancer related incidence and	B	**Substantial**
mortality were seen in a single randomised controlled trial, and also in the pooled data from several trials, and only after almost 2 decades of follow-up.	C	**Moderate**
Those taking aspirin also experienced significant adverse effects including gastrointestinal bleed and symptoms.	D	**Slight/Restricted**

High risk population
Although these trials did not report mortality data, and reported follow-up of 5 years or less, aspirin was reported to be reduce colorectal cancer incidence in only the CAPP2 trial, and only after per-protocol analysis. Reduction in the risk of adenoma and advanced lesion was reported in the AFPPS, APACC, CALGB, and ukCAP trials, and lower daily doses of aspirin (≤160mg/day) was most beneficial for adenomas, and higher daily aspirin doses (300-325 mg/day) was most beneficial in reducing the risk of advanced lesions.

In general terms, the data above do not include the drop-out rate of participates in the aspirin arm of these trials, mainly due to aspirin adverse effects. The above data also do not include any benefits aspirin may also have at reducing cardiovascular disease events and/or mortality in the same elderly population. If the dose for chemoprevention of cancer can be defined as the same as the dose for cardiovascular protection, the case for more general use of aspirin in the community will be strong – especially for those with risk factors either for colorectal cancer and/or cardiovascular disease. **Grade C** (low risk population) **Grade B** (high risk population)		

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*

Low risk population	A	**Evidence directly generalisable to target population**
All clinical trials were conducted in western populations, with the majority based on European populations, except for the WHS trial which was from a USA population and only in women, and the SALT trial from Sweden. All trials had a population at randomisation with a mean/median age >50 years. None of the trials is directly generalizable to the Australian average risk population though the WHS comes close; its limitation is that was average risk women only. **Grade B** *High risk population* All clinical trials were conducted in western populations, with the AFPPS and CALGB trials based in North America, and the APACC and ukCAP trials based in Europe. The CAPP2 trial included study centres in six geographic locations, including Australia. **Grade B**	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

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

The evidence is directly applicable to the Australia health care system, as aspirin is widely available, cheap and almost certainly effective. There would however need to be caveats for people with a history of peptic ulcer, dyspepsia, uncontrolled hypertension, allergy to aspirin or renal impairment. **Grade A**	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**

	D	**Evidence not applicable to Australian healthcare context**

Other factors *(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).*

A limitation to these trials that specifically included average (or low) risk populations is that none of them had colorectal cancer as the primary endpoint, and none were colonoscopically controlled. All participants in the high-risk populations trials (CAPP2, AFPPS, APACC, CALGB, and ukCAP) had colonoscopic examination prior to entry into these studies. Most studies did not report on aspirin exposure after the randomised interventional period. The WHS trial did have cancer as a primary endpoint (any invasive cancer, excluding non-melanoma skin cancer), but the incidence of colorectal cancer was a secondary endpoint. All of these trials document the adverse effects well during intervention but less well during the long periods of follow up that were needed to define the cancer incidence and mortality rates.

In general terms, the data above do not include the drop-out rate of participates in the aspirin arm of these trials, mainly due to aspirin adverse effects. The above data also do not include any benefits aspirin may also have at reducing cardiovascular disease events and/or mortality in the same elderly population. All trials included participants with a mean age ranging from 55-60±7 years (SD), except for the CAPP2 trial which include participants aged from 25-79 years. If the dose for chemoprevention of cancer can be defined as the same as the dose for cardiovascular protection, the case for more general use of aspirin in the community will be strong – especially for those with risk factors either for colorectal cancer and/or cardiovascular disease. Although not part of this systematic review, meta-analyses of large numbers of cohort studies have shown that regular use of aspirin was associated with reduced risk of colorectal cancer (pooled odds ratio 0.62, 95% CI 0.58-0.67, p<0.0001)(Algra et al., 2012)(Lancet Oncol 2012; 13: 518–27)

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.

Component	Rating	Description
1. Evidence base	**B** **A**	Low risk population - Four level II studies at low risk of bias, and one level II study at high risk of bias. High risk population - Five level II studies at low risk of bias.
2. Consistency	**B, B** **B, N/A** **A, N/A**	Grade B – Colorectal cancer incidence (low risk population) Grade B – Colorectal cancer incidence (high risk population) Grade B – Colorectal cancer mortality (low risk population) Grade N/A – Colorectal cancer mortality (high risk population) Grade A – Adverse effects (low risk population) Grade N/A – Adverse effects (high risk population)
3. Clinical impact	**C, B**	Grade B - Low risk population (Moderate) Grade B - High risk population (Substantial)

| 4. Generalisability | **B, B** | Evidence directly generalisable to target population with some caveats (low and high risk populations) |
| 5. Applicability | **A** | Evidence directly applicable to Australian healthcare context (low and high risk populations) |

Evidence statements:

Average-risk population:

Colorectal cancer incidence and mortality

In the post hoc analyses of the cardiovascular prevention trials, predominantly in males, there was evidence for a real but small reduction in incidence and mortality from colorectal cancer commencing 10 years after starting aspirin.

Evidence from all trials showed a significant reduction in the incidence of proximal colon cancer compared to distal colon cancer in those taking aspirin. Benefit is attenuated distally.

It is not known if the colorectal cancer risk reduction and mortality reduction benefits can be extrapolated to populations without cardiovascular risk. The risk of aspirin in these average risk settings still needs more empirical data.

Aspirin commencement age

Most of the studies recruited participants aged 50 years or older. Based on the age range of recruitment into the trials, the evidence supported commencing aspirin between the ages of 50 and 70 years.

Aspirin duration

Taking aspirin for 2.5 years was shown to be just as effective as taking it for 5 years, when considering colorectal cancer incidence and mortality, but only after a latent period of 10 years. The benefit extends to older ages with longer duration of use.

Aspirin dose and frequency

A low dose of aspirin (100–300 mg per day) is as effective at reducing colorectal mortality as a higher dose.

Potential harms of aspirin

Aspirin was shown to be associated with increased incidence of the following adverse events:
- dyspepsia
- peptic ulcer
- bleeding diathesis
- gastrointestinal haemorrhage (such as associated with use of oral anticoagulants or antiplatelet agents).

Aspirin should be avoided in those with:
- aspirin allergy
- renal impairment.

Overall health benefit over harm
The overall health benefit over risk depends on the likelihood of a clinically significant bleeding risk, particularly gastrointestinal and intracerebral haemorrhage.
The likelihood of health benefit was 5 times greater than the health harm.
The likelihood of preventing death is 5 to 10 times greater than the likelihood of causing death.

Aspirin demonstrated a benefit in reducing thrombotic strokes.

Sex and age considerations
The evidence reported from the cardiovascular risk trials was from a predomintantly male population (92%).

In the only trial conducted in an average-risk population with cancer as the primary endpoint (which recruited only women at average risk of cardiovascular disease and cancer), there was evidence of colorectal cancer prevention in women under 65 years taking alternate-day 100 mg aspirin. There was a suggestion of overall health benefit in women over 65 years, but not from colorectal cancer prevention.

High-risk population:
Colorectal cancer incidence and mortality
In the high-risk population (notably, people with Lynch Syndrome), benefits for aspirin compliers were unequivocally greater than risks.

Aspirin dose and frequency
The dose demonstrated in the pivotal CAPP2 trial was 600 mg daily taken for at least 2 years.

Adverse events
The only adverse event reporting a significant reduction in participants on aspirin compared to placebo was stroke. The CAPP2 trial did not report statistical analysis of serious adverse events but numerically there was no difference in adverse outcomes.

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

Evidence based recommendation #1:

For all people aged 50–70 years who are at average risk of colorectal cancer, aspirin should be actively considered to prevent colorectal cancer. A low dose (100–300 mg per day) is recommended for at least 2.5 years, commencing at age 50 to 70 years. The benefit may extend to older ages with longer duration of use. Benefit for cancer prevention (though shorter for cardiovascular risk) is evident only 10 years after initiaton so a life expectancy of at least 10 years should be taken into consideration in the advice to use aspirin.

The choice to take aspirin should be personalised based on age, sex and potential reduction in cardiovascular events, cerebrovascular events and thrombotic stroke. The individual should take into account the potential risks of taking aspirin. Aspirin should be avoided in patients with current

dyspepsia, any history of peptic ulcer, aspirin allergy, bleeding diathesis, an increased risk of gastrointestinal haemorrhage (such as associated with use of oral anticoagulants or antiplatelet agents), or renal impairment.

The benefit in colorectal cancer risk reduction in women over 65 is less clear cut; however with the limited data available, those older women with cardiovascular risk factors may derive a greater overall benefit than harm.
Grade B

Evidence based recommendation #2:
People who are at high risk of colorectal cancer due to Lynch Syndrome carrier status should be advised to begin aspirin from the commencement of their colonoscopy screening (usually at age 25 years).
Grade A

Evidence based recommendation #3:
Non-syndromic familial cancer patients should be actively considered for aspirin, bearing in mind the possibility of adverse events.

600 mg/day has shown to be effective, but lower dose (100 mg/day) may be as effective and is recommended based on the data available at the time of the systematic review.
Grade B

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

Practice points:

- Aspirin should be avoided in patients with uncontrolled hypertension.

- Breath testing for *Helicobacter pylori* (and treatment for those who test positive) can also be considered, as gastrointestinal toxicity from aspirin is enhanced in the presence of *Helicobacter pylori*.

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.
The following issues are unresolved: • The optimal dose for colorectal cancer protection (100 mg/day, 300 mg/day or 600 mg/day) has not been identified. More data are needed before specific recommendations can be made. • There is a lack of RCTs of aspirin in average-risk populations with CRC as the primary endpoint. • There is no information on aspirin use in the elderly. • There is no information on the optimal target age range (including starting and stopping ages) for aspirin use in average-risk populations. • Better analysis is needed of dose-related risk versus benefit of aspirin use stratified by age as the balance of benefit and harm is unknown in those of 70 years.

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? There will be a more widespread recognition of the chemopreventative benefits of aspirin.	**YES**
Are there any resource implications associated with implementing this recommendation? Education for GPs on the risks and benefits will be needed to engage their support for the recommendations. Renal function will need to be measured if there is doubt about aspirin usage. It is anticipated most dispensing will be over the counter and user paid (rather than reimbursed by the Pharmaceutical Benefits Scheme).	**YES**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**YES**

This will take some broad educational approach to the profession and through public education.	