National Institute for Health and Care Excellence

Draft for consultation

Colorectal cancer (update)

[A1] Effectiveness of aspirin in the prevention of colorectal cancer in people with Lynch syndrome

NICE guideline TBC

Evidence reviews

July 2019

Draft for consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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ISBN:

Contents

1

The effectiveness of aspirin in the prevention of colorectal cancer in people with Lynch syndrome

This evidence review supports recommendation 1.1.1.

Review question

How effective is aspirin in the prevention of colorectal cancer in adults with Lynch syndrome (hereditary nonpolyposis colorectal cancer)?

Introduction

Lynch syndrome, previously known as hereditary nonpolyposis colorectal cancer (or HNPCC), is a hereditary genetic condition predisposing its carriers to high risk of colorectal cancer as well as other forms of cancer. It is caused by a germline mutation in the DNA mismatch repair (MMR) gene. An estimated 175,000 people in the UK have Lynch syndrome and it is estimated that annually over 1,100 colorectal cancers are diagnosed among carriers of Lynch syndrome in the UK. The lifetime risk of colorectal cancer in people with Lynch syndrome is estimated to be up to 80%.

The main strategy to prevent colorectal cancer in people with Lynch syndrome has been regular screening with colonoscopy and polypectomy. Aspirin has been suggested as another potential prevention strategy for colorectal cancer.

Therefore, the aim of this review is to determine if aspirin is effective as prevention of colorectal cancer in people with Lynch syndrome.

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 Lynch syndrome (hereditary nonpolyposis colorectal cancer)
Intervention	Oral aspirin (all dosages, all durations)
Comparison	• Placebo/no intervention • Different durations of aspirin intake
Outcomes	**Critical** • Overall survival • Development of colorectal cancer • Development of non-colorectal Lynch syndrome-related cancers **Important** • Development of colorectal adenomas • Adverse events - any Grade 3 or 4 adverse event, haemorrhagic stroke, gastrointestinal bleeding, peptic ulcer, treatment-related mortality

For further details see the review protocol in appendix A.

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

One randomised controlled trial (RCT) and 1 retrospective cohort study (3 publications) were included in this evidence review (CAPP2 trial [Burn 2008, Burn 2011], Ouakrim 2015).

The included studies are summarised in Table 2.

The CAPP2 trial compared aspirin to placebo (CAPP2 trial [Burn 2008, Burn 2011]) and the retrospective cohort study compared aspirin to never using aspirin (Ouakrim 2015).

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 studies

Study	Population	Intervention/Comparison	Outcomes
CAPP2 trial (Burn 2008; Burn 2011) RCT Australia, Denmark, Finland, France, Germany, Hong Kong, Italy, the Netherlands, Poland, South Africa, Sweden, UK, US	Proven carriers of a pathologic mismatch-repair mutation ("genetic diagnosis") 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 ('clinical diagnosis'), older than 25 years of age. N=1071 randomised N=937 received intervention	Aspirin 600 mg per day versus placebo	• Development of neoplasia (colorectal adenoma or carcinoma) • Development of adenoma only • Development of colorectal cancer only • Development of adenoma and colorectal cancer • Development of advanced adenoma or colorectal cancer • Non-colorectal Lynch syndrome-related cancers • All Lynch-syndrome cancers • Adverse events:

Study	Population	Intervention/Comparison	Outcomes
			○ Cerebral haemorrhage ○ Gastrointestinal bleeding ○ Gastric ulcer ○ Duodenal ulcer ○ Probable or possible peptic ulcer ○ Serious adverse event
Ouakrim 2015 Retrospective cohort study Australia, Canada, New Zealand, US	Proven carriers of mismatch-repair gene mutation N=1858	Aspirin use at least twice a week for 1 month or longer (1 month to 4.9 years and 5 years or more) versus never using aspirin	• Colorectal cancer

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 outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

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: Aspirin versus placebo

Critical outcomes

Overall survival

No evidence was identified to inform this outcome.

Development of colorectal cancer

- There is moderate quality evidence from 1 RCT (N=861; mean follow-up 4.6 years) using intention-to-treat analysis that there is no clinically important effect of aspirin on the development of colorectal cancer at 5 years compared to placebo in people with Lynch syndrome.
- There is low quality evidence from 1 RCT (N not specified; mean follow-up 4.6 years) using per-protocol subgroup analysis that there is no clinically important effect of aspirin taken for less than 2 years on the development of colorectal cancer compared to placebo taken for 2 or more years in people with Lynch syndrome.
- There is low quality evidence from 1 RCT (N not specified; mean follow-up 4.6 years) using per-protocol subgroup analysis that aspirin taken for 2 or more years produces a clinically important decrease in the development of colorectal cancer compared to placebo taken for 2 or more years in people with Lynch syndrome.

Development of non-colorectal Lynch syndrome-related cancer

- There is moderate quality evidence from 1 RCT (N=861; mean follow-up 4.6 years) using intention-to-treat analysis that there is no clinically important effect of aspirin on the development of non-colorectal Lynch syndrome-related cancer compared to placebo in people with Lynch syndrome.
- There is low quality evidence from 1 RCT (N not specified; mean follow-up 4.6 years) using per-protocol subgroup analysis that there is no clinically important effect of aspirin taken for less than 2 years on the development of non-colorectal Lynch syndrome-related cancer compared to placebo taken for 2 or more years in people with Lynch syndrome.
- There is low quality evidence from 1 RCT (N not specified; mean follow-up 4.6 years) using per-protocol subgroup analysis that there is no clinically important effect of aspirin taken for 2 or more years on the development of non-colorectal Lynch syndrome-related cancer compared to placebo taken for 2 or more years in people with Lynch syndrome.

Development of any Lynch syndrome-related cancer

- There is moderate quality evidence from 1 RCT (N=861; mean follow-up 4.6 years) using intention-to-treat analysis that there is no clinically important effect of aspirin on the development of any Lynch syndrome-related cancer at 5 years compared to placebo in people with Lynch syndrome.
- There is low quality evidence from 1 RCT (N not specified; mean follow-up 4.6 years) using per-protocol subgroup analysis that there is no clinically important effect of aspirin taken for less than 2 years on the development of any Lynch syndrome-related cancer compared to placebo taken for 2 or more years in people with Lynch syndrome.
- There is low quality evidence from 1 RCT (N not specified; mean follow-up 4.6 years) using per-protocol subgroup analysis that aspirin taken for 2 or more years produces a clinically important decrease in the development of any Lynch syndrome-related cancer compared to placebo taken for 2 or more years in people with Lynch syndrome.

Important outcomes

Development of colorectal adenoma

- There is low quality evidence from 1 RCT (N=693; mean follow-up 2.4 years) using per-protocol analysis (adjusted for number of colonoscopies) that there is no clinically important effect of aspirin on the development of colorectal adenoma or colorectal cancer compared to placebo in people with Lynch syndrome.
- There is low quality evidence from 1 RCT (N=693; mean follow-up 2.4 years) using per-protocol analysis (adjusted for number of colonoscopies) that there is no clinically

important effect of aspirin on the development of advanced colorectal adenoma or colorectal cancer compared to placebo in people with Lynch syndrome.

- There is low quality evidence from 1 RCT (N=693; mean follow-up 2.4 years) using per-protocol analysis (adjusted for number of colonoscopies) that there is no clinically important effect of aspirin on the development of colorectal adenoma only compared to placebo in people with Lynch syndrome.

Adverse events

- There is low quality evidence from 1 RCT (N=861; mean follow-up 4.6 years) that there is no clinically important effect of aspirin on the risk of severe adverse events during intervention compared to placebo in people with Lynch syndrome.
- There is low quality evidence from 1 RCT (N=861; mean follow-up 4.6 years) that there is no clinically important effect of aspirin on the risk of gastrointestinal bleeding during intervention compared to placebo in people with Lynch syndrome.
- There is low quality evidence from 1 RCT (N=861; mean follow-up 4.6 years) that there is no clinically important effect of aspirin on the risk of duodenal ulcer during intervention compared to placebo in people with Lynch syndrome.
- There is low quality evidence from 1 RCT (N=861; mean follow-up 4.6 years) that there is no clinically important effect of aspirin on the risk of probable or possible peptic ulcer during intervention compared to placebo in people with Lynch syndrome.
- There is low quality evidence from 1 RCT (N=861; mean follow-up 4.6 years) that there is no clinically important effect of aspirin on the risk of cerebral haemorrhage during intervention compared to placebo in people with Lynch syndrome.
- There is low quality evidence from 1 RCT (N=861; mean follow-up 4.6 years) that there is no clinically important effect of aspirin on the risk of gastric ulcer during intervention compared to placebo in people with Lynch syndrome.

Comparison 2: Aspirin versus never aspirin

Critical outcomes

Overall survival

No evidence was identified to inform this outcome.

Development of colorectal cancer

- There is low quality evidence from 1 retrospective cohort study (N=1858; mean follow-up 16.3 years) that aspirin use produces a clinically important decrease on the development of colorectal cancer compared to never use of aspirin in people with Lynch syndrome.
- There is low quality evidence from 1 retrospective cohort study (N=1858; mean follow-up 16.3 years) that aspirin use for 1 month to 4.9 years produces a clinically important decrease on the development of colorectal cancer compared to never use of aspirin in people with Lynch syndrome.
- There is low quality evidence from 1 retrospective cohort study (N=1858 mean follow-up 16.3 years) that aspirin use for 5 or more years produces a clinically important decrease on the development of colorectal cancer compared to never use of aspirin in people with Lynch syndrome.

Development of non-colorectal Lynch syndrome-related cancer

No evidence was identified to inform this outcome.

Important outcomes

Development of colorectal adenomas

No evidence was identified to inform this outcome.

Adverse events

No evidence was identified to inform this outcome.

Economic evidence statements

No economic evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

This review aimed to find out whether aspirin prevents colorectal cancer in people with Lynch syndrome. Therefore, the incidence of colorectal cancer was a critical outcome for decision making. People with Lynch syndrome are also at an increased risk of other cancers and the incidence of non-colorectal Lynch syndrome-related cancers was also a critical outcome. Overall survival was also a critical outcome for decision making.

Development of colorectal adenomas and adverse events, more specifically grade 3 or 4 adverse events, cerebral haemorrhage, gastrointestinal bleeding, peptic ulcer and treatment-related mortality, were considered important outcomes.

The quality of the evidence

Evidence was available for the comparison of aspirin versus placebo and aspirin use versus no aspirin use. Evidence was available for all of the outcomes except overall survival and treatment-related mortality.

The quality of the clinical evidence was assessed using GRADE and varied from low to moderate quality.

The included RCT had a relatively low number of events and therefore the effect estimates were imprecise. Per protocol analysis was performed and reported for some outcomes instead of the more appropriate intention-to-treat analysis. The population in the RCT consisted mainly of people with pathologic evidence of having Lynch syndrome (meaning they were carriers of a mismatch repair gene mutation), however, a proportion of the population (around 18%) were people with a 'clinical diagnosis' of Lynch syndrome. 'Clinical diagnosis' was defined using the modified Amsterdam criteria. The committee agreed that although this type of diagnosis of Lynch syndrome is outdated, it is unlikely to affect the results in any significant way.

The effect estimates from the observational evidence were considered more precise because of larger sample size and higher number of events. However, the quality of the evidence from the retrospective cohort study was downgraded due to a high risk of recall bias in relation to the use of aspirin. However, this data showed a dose response effect: longer use of aspirin (5 or more years) showed lower rates of colorectal cancer than shorter use of aspirin (1 month to 4 years). This improves confidence in the evidence of a beneficial effect of aspirin in this population.

Benefits and harms

The beneficial effect of aspirin in people with Lynch Syndrome is in the prevention of colorectal or other Lynch syndrome cancers and their related morbidity and mortality. Evidence from the per-protocol analysis of the included RCT suggested that on average 30 people with Lynch Syndrome would have to take aspirin for 2 or more years (instead of placebo) to prevent one additional case of colorectal cancer within the first 5 years after treatment. There was however no clinically important effect among people who used aspirin for less than 2 years, or in the intention-to-treat analysis.

The committee also considered a secondary analysis of incidence rates (allowing for multiple cancers per individual) in the included RCT and evidence from the observational study included in the review which demonstrated a beneficial effect of aspirin in preventing colorectal cancer. The beneficial effect of aspirin in the observational study was especially large in people who had taken aspirin for 5 or more years

The potential harm of aspirin use is excess bleeding, such as peptic ulcer, gastrointestinal bleeding or cerebral haemorrhage with the risk increasing with age. Evidence of adverse events from CAPP2 trial found no difference in the occurrence of adverse events between aspirin and placebo groups. This data was, however, only collected during the intervention period (2 years) and not during the follow-up. There was also no age-stratified data available to assess the risk in older participants. Therefore, there is uncertainty about the long-term adverse effects of aspirin use among people with Lynch syndrome. The potential harms and benefits of long-term aspirin use should be discussed with the person with Lynch syndrome so that they can make an informed decision about its use.

The committee also discussed whether proton pump inhibitors should be recommended alongside aspirin in order to reduce gastrointestinal risks. However, the CAPP2 trial found no increase in adverse events in the aspirin group. In addition, to the committee's knowledge there is no convincing evidence from other RCT data that proton pump inhibitors should be used alongside aspirin for primary prophylaxis of gastrointestinal bleeding. Proton pump inhibitors are relatively costly and may be overprescribed in current practice. The committee was aware that other guidelines recommend testing for Helicobacter pylori, and eradication of it if present, before commencing aspirin because it increases the risk of peptic ulcer. This was, however, outside the remit of this review.

The optimal dose of aspirin remains unclear and the committee was not able to recommend a dose for aspirin. The CAPP2 trial used a high dose of 600mg of aspirin per day whereas the observational study had smaller doses (varying self-reported doses). A higher dose could potentially increase the risk of adverse effects, whereas a smaller dose might not be effective in prevention of colorectal cancer. An ongoing CAPP3 trial studies the optimal dose of aspirin for prevention of colorectal cancer in people with Lynch syndrome comparing 100 mg, 300 mg and 600 mg doses. A commonly used dose in current practice is either 150 mg (75 mg x 2) or 300 mg, sometimes depending on other gastrointestinal risk factors.

The committee recognised that in the presence of any contraindications for aspirin, its use should be avoided.

Considering the clinical evidence and weighing the benefits and harms of aspirin use, the committee agreed that aspirin use for at least 2 years should be considered in people with Lynch syndrome. Future evidence is expected to clarify the uncertainties regarding the benefits and harms of its use and the optimal dose of aspirin in prevention of colorectal cancer.

Cost effectiveness and resource use

No economic evidence was identified that addressed this topic.

It was thought that the use of aspirin was likely to be cost-effective given the very small drug costs and administration costs. Furthermore, the recommendation is likely to have a minimal resource impact because aspirin is already widely used for this indication in current practice.

Other factors the committee took into account

Evidence on its use among the general population seems to suggest that aspirin has a preventative effect on colorectal cancer. The Women's Health Study, the only large-scale RCT studying the preventative effect of aspirin on cancer, initially found no effect at 10 years of follow-up (Cook 2005). However, after 18 years of follow-up, a beneficial effect of aspirin on colorectal cancer, particularly proximal colon cancer, was found (Cook 2013). Previously, RCTs examining the effect of aspirin on cardiovascular events have shown that aspirin users had a lower incidence of colorectal cancer and observational studies seem to support this (Algra and Rothwell 2012).

A recent review on the benefits and harms of aspirin use in preventing cancer in the general population conclude that the benefits of taking 75 to 325mg of aspirin per day for at least 5 years overrides the harms and the longer the use, the greater the effect (Cuzick 2015). The Women's Health Study conducted among the general population women found more gastrointestinal bleeding and peptic ulcers in the aspirin group (Cook 2013).

A recent review among the general population did not find a difference in effect across different doses indicating that higher dose of aspirin does not add benefit but instead increases the harmful effects (Cuzick 2015). An ongoing CAPP3 trial is currently studying the optimal dose of aspirin for prevention of colorectal cancer in people with Lynch syndrome.

References

Algra and Rothwell 2012

Algra A and Rothwell P (2012) Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncology 13(5): 518-27

CAPP2 trial

Burn J, Bishop D, Mecklin J, et al. (2008) Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome. New England Journal of Medicine 359(24): 2567-78

Burn J, Gerdes A, Mecklin J, et al. (2011) Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 378(9809): 2081-7

Cook 2013

Cook N, Lee I, Zhang S, et al. (2013) Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. Annals of Internal Medicine 159(2): 77-85

Cook 2005

Cook N, Lee I, Gaziano J, et al. (2005) Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. Journal of the American Medical Association 294(1): 47-55

Cuzick 2015

Cuzick J, Thorat M, Bosetti C, et al. (2015) Estimates of benefits and harms of prophylactic use of aspirin in the general population. Annals of Oncology 26(1): 47-57

Ouakrim 2015

1 Ouakrim D, Dashti S, Chau R, et al. (2015) Aspirin, Ibuprofen, and the risk for colorectal
2 cancer in Lynch Syndrome. Journal of the National Cancer Institute 107(9): pii: djv170

3

Appendices

Appendix A – Review protocol

Review protocol for review question: What is the effectiveness of aspirin in the prevention of colorectal cancer in people with Lynch syndrome?

Table 3: Review protocol for the effectiveness of aspirin in the prevention of colorectal cancer in people with Lynch syndrome

Field (based on PRISMA-P)	Content
Review question	How effective is aspirin in the prevention of colorectal cancer in adults with Lynch syndrome (hereditary nonpolyposis colorectal cancer)?
Type of review question	Intervention
Objective of the review	To determine whether aspirin is effective in preventing the development of colorectal cancer in adults with Lynch syndrome.
Eligibility criteria – population/disease/condition/issue/domain	Adults with Lynch syndrome (hereditary nonpolyposis colorectal cancer)
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Oral aspirin (all dosages, all durations)
Eligibility criteria – comparator(s)/control or reference (gold) standard	Comparisons: • Placebo/no intervention • Different durations of aspirin intake

Outcomes and prioritisation	Critical:
	• Overall survival (minimally important difference [MID]: statistical significance)
	• Development of colorectal cancer (MID: statistical significance)
	• Development of non-colorectal Lynch syndrome-related cancers (MID: statistical significance)
	
	Important:
	• Development of colorectal adenomas (MID: statistical significance)
	• Adverse events
	  ○ Any Grade 3 or 4 adverse event – re-intervention or multi-organ failure as reported in individual studies (MID: statistical significance)
	  ○ Haemorrhagic stroke (MID: statistical significance)
	  ○ Gastrointestinal bleeding (MID: statistical significance)
	  ○ Peptic ulcer (MID: statistical significance)
	  ○ Treatment-related mortality (MID: statistical significance)

Eligibility criteria – study design	• Systematic reviews of RCTs • RCTs

Field (based on PRISMA-P)	Content
	• If eligible RCTs are not available: prospective cohort studies • If eligible prospective cohort studies are not available: retrospective cohort studies
Other inclusion exclusion criteria	Inclusion: • English-language • All settings will be considered that consider medications and treatments available in the UK • Studies published post 1997 Studies conducted post 1997 will be considered for this review question, as the GC felt that significant advances have occurred in the in the diagnosis of Lynch syndrome since this time period and outcomes for adults with Lynch syndrome prior to 1997 are not the same as post 1997.
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analysis will be done in the following subgroups: • Mismatch repair gene mutation carriers (genetic evidence) • People with no previous Lynch syndrome-related cancer/people with previous Lynch syndrome-related cancer • According to age at starting and stopping aspirin treatment In the case of high heterogeneity in the meta-analysis of critical outcomes, the following factors/subgroups will be considered: • Dose of aspirin • Surveillance tests used
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 and data extraction will not be undertaken for this question.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). '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 (to be confirmed by the Information Scientist): 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 1997
Identify if an update	Not an update
Author contacts	Developer: NGA https://www.nice.org.uk/guidance/indevelopment/gid-ng10060

Field (based on PRISMA-P)	Content
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	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in 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 • ROBINS-I tool for non-randomised studies 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	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 reports both, the method used in the majority of studies will be analysed. Minimally important differences (MIDs): The guideline committee identified statistically significant differences as appropriate indicators for clinical significance for all outcomes except quality of life for which published MIDs from literature will be used (see outcomes section for more information).
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods and process section of the main file
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.

Field (based on PRISMA-P)	Content
	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 please 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 NGA 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 to PROSPERO

AMSTAR: A Measurement Tool to Assess Systematic Reviews; CCTR: Cochrane Controlled Trials Register; CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: Minimally important difference; NGA: National Guideline Alliance; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols; PROSPERO: International Prospective Register of Systematic Reviews; RCT: randomised controlled trial; ROBINS-I: Risk of Bias in Non-randomised Studies – of Interventions

1 Appendix B – Literature search strategies

2 Literature search strategies for review question: What is the effectiveness of 3 aspirin in the prevention of colorectal cancer in people with Lynch syndrome?

4 Databases: Embase/Medline

5 Last searched on: 24/10/2017

#	Search
1	exp Colorectal Neoplasms, Hereditary Nonpolyposis/ or exp Adenomatous Polyposis Coli/
2	1 use prmz
3	exp hereditary nonpolyposis colorectal cancer/ or exp colon polyposis/
4	3 use oemezd
5	(Hereditary Nonpolyposis Colorectal Cancer or HNPCC or lynch syndrome).ti,ab.
6	2 or 4 or 5
7	exp Aspirin/ or exp Anticarcinogenic Agents/ or exp Anti-Inflammatory Agents, Non-Steroidal/ or exp Antineoplastic Agents/ or exp Chemoprevention/ or exp Drug Therapy, Combination/ or exp Starch/
8	7 use prmz
9	exp acetylsalicylic acid/ or exp antineoplastic agent/ or exp nonsteroid antiinflammatory agent/ or exp chemoprophylaxis/ or exp combination drug therapy/ or exp starch/
10	9 use oemezd
11	(aspirin or acetylsalicylic acid or anticarcinog* or anti?inflammat* or NSAID* or antineoplas* or chemoprevent* or chemoprophyla* or starch).ti,ab.
12	8 or 10 or 11
13	6 and 12
14	exp colon cancer/dt, pc or exp rectum cancer/dt, pc
15	14 use oemezd
16	exp Colorectal Neoplasms/dt, pc
17	16 use prmz
18	15 or 17
19	exp aspirin/
20	19 use prmz
21	exp acetylsalicylic acid/
22	21 use oemezd
23	20 or 22
24	18 and 23
25	13 or 24
26	limit 25 to english language
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	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.
41	40 use prmz
42	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.
43	42 use oemezd
44	or/41,43
45	26 not 39
46	44 and 45
47	epidemiologic studies/ or observational study/ or case control studies/ or retrospective studies/ or cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or cross-sectional studies/
48	47 use prmz

#	Search
49	exp observational study/ or exp case control study/ or exp retrospective study/ or exp cohort analysis/ or exp longitudinal study/ or exp follow up/ or exp prospective study/ or exp cross-sectional study/
50	49 use oemezd
51	((retrospective* or cohort* or longitudinal or follow?up or prospective or cross section*) adj3 (stud* or research or analys*)).ti.
52	48 or 50 or 51
53	45 and 52
54	limit 53 to yr="1997 -Current"
55	46 or 54

1 **Database: Cochrane Library**

2 Last searched on: 25/10/2017

#	Search
1	MeSH descriptor: [Colorectal Neoplasms, Hereditary Nonpolyposis] explode all trees
2	MeSH descriptor: [Adenomatous Polyposis Coli] explode all trees
3	Hereditary Nonpolyposis Colorectal Cancer or HNPCC or lynch syndrome
4	#1 or #2 or #3
5	MeSH descriptor: [Aspirin] explode all trees
6	MeSH descriptor: [Anticarcinogenic Agents] explode all trees
7	MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees
8	MeSH descriptor: [Antineoplastic Agents] explode all trees
9	MeSH descriptor: [Chemoprevention] explode all trees
10	MeSH descriptor: [Drug Therapy, Combination] explode all trees
11	MeSH descriptor: [Starch] explode all trees
12	aspirin or acetylsalicylic acid or anticarcinog* or anti?inflammat* or NSAID* or antineoplas* or chemoprevent* or chemoprophyla* or starch
13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
14	#4 and #13
15	MeSH descriptor: [Colorectal Neoplasms] explode all trees and with qualifier(s): [Drug therapy - DT, Prevention & control - PC]
16	#5 and #15
17	#14 or #16

3 **Database: Web of Science**

4 Last searched on: 25/10/2017

#	Search
5	(#4) *AND* **LANGUAGE:** (English)
4	#2 AND #1 Refined by: **DOCUMENT TYPES:** (ARTICLE OR REVIEW)
3	#2 AND #1
2	ts=aspirin or ts=acetylsalicylic acid or ts=anticarcinog* or ts=anti?inflammat* or ts=NSAID* or ts=antineoplas* or ts=chemoprevent* or ts=chemoprophyla* or ts=starch or ts=combination drug therapy
1	ts=Hereditary Nonpolyposis Colorectal Cancer or ts=HNPCC or ts=lynch syndrome or ts=Adenomatous Polyposis Coli

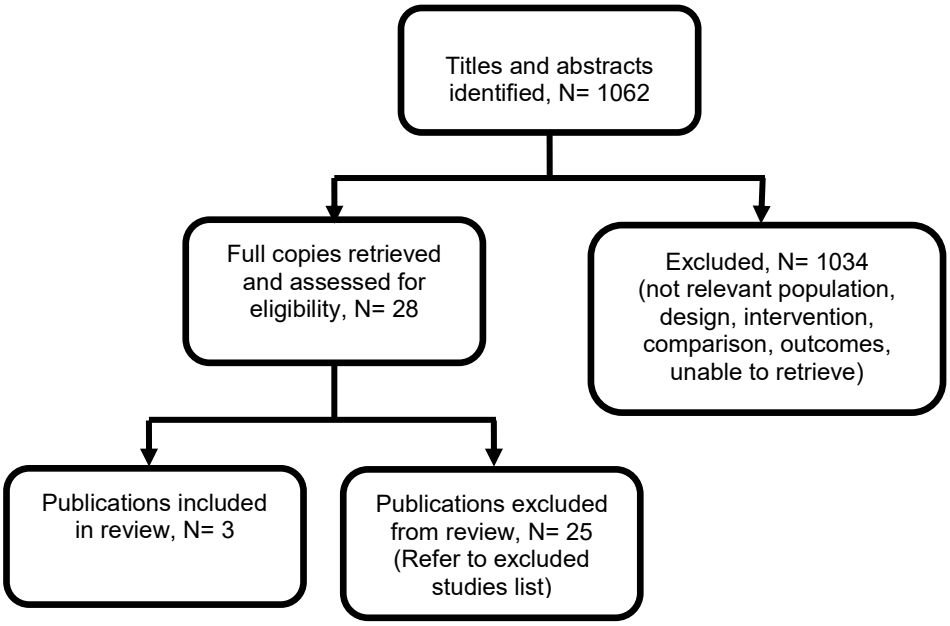
5

6

Appendix C – Clinical evidence study selection

Clinical study selection for: What is the effectiveness of aspirin in the prevention of colorectal cancer in people with Lynch syndrome?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is the effectiveness of aspirin in the prevention of colorectal cancer in people with Lynch syndrome?

Table 4: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Burn, J, Bishop, Dt, Mecklin, Jp, Macrae, F, Möslein, G, Olschwang, S, Bisgaard, Ml, Ramesar, R, Eccles, D, Maher, Er, Bertario, L, Jarvinen, Hj, Lindblom, A, Evans, Dg, Lubinski, J, Morrison, Pj, Ho, Jw, Vasen, Hf, Side, L, Thomas, Hj, Scott, Rj, Dunlop, M, Barker, G, Elliott, F, Jass, Jr, Fodde, R, Lynch, Ht, Mathers, Jc, Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome, New England Journal of MedicineN Engl J Med, 359, 2567-2578, 2008 **Ref id** 702413 **Country/ies where the study was carried out:** Australia, Denmark, Finland, France, Germany, Hong Kong,	**Sample size** N=1071 randomised. N=937 received study drug N=746 included in outcome analysis N=350 received aspirin and included in outcome analysis N=343 received placebo and included in outcome analysis. **Characteristics** Participants recruited and received study intervention Age at study entry, mean (range): 45 years (25-79) Sex: 56% female, 44% male Clinical diagnosis: 17.4% Genetic diagnosis: 82.6% Mutation: 60% MLH1, 37% MSH2, 3% MSH Geographic region: 45% Northern	**Interventions** Aspirin 600 milligrams per day versus placebo. The trial also included an intervention to give resistant starch or placebo, therefore, participants were randomly assigned to either: aspirin+placebo, aspirin+starch, starch+placebo, or placebo+placebo Participants also had an option to be allocated to a single intervention only. For this analysis the aspirin only, aspirin+placebo and aspirin+starch groups were combined into the *aspirin group* and	**Details** Randomisation - Randomisation was computer-generated. It was done in blocks of 16 separately for six geographical groups of participating centres to ensure balance across the intervention arms. Allocation concealment Not reported. Blinding - The participants and the investigators were blinded for the study group allocations. Follow-up - Primary outcome: detection of at least one adenoma or colorectal carcinoma Secondary outcomes: detection of an adenoma only, colorectal cancer only, adenoma and colorectal cancer, and advanced adenoma or	**Results** Development of neoplasia (colorectal adenoma or carcinoma) at mean 29 months of follow-up Placebo: 65/343 Aspirin: 66/350 Crude HR 1.1 95% CI 0.8 to 1.5 Adjusted HR 1.0 95% CI 0.7 to 1.5 (adjusted for number of colonoscopic examinations) Development of adenoma only at mean 29 months of follow-up Placebo: 55/343 Aspirin: 56/350 Development of colorectal cancer only at mean 29 months of follow-up Placebo: 7/343 Aspirin: 5/350	**Limitations -** Cochrane risk of bias tool Selection bias Random sequence generation: low risk Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: low risk Detection bias Blinding of outcome assessment: low risk Attrition bias Incomplete outcome data: high risk of bias (Per-protocol analysis performed, 30% of the originally randomised were not included in the analysis.) Reporting bias Selective reporting: unclear risk of bias (The main analysis in the paper reports the main outcomes combined

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Italy, the Netherlands, Poland, South Africa, Sweden, UK, US. **Study type** RCT (CAPP2 trial, ISRCTN59521990) **Aim of the study** To estimate the effect of aspirin on preventing colorectal neoplasia in people with Lynch syndrome. **Study dates** Intervention was started by participants between January 1999 and March 2005 (reported by Burn et al. 2011). The participants received the study drugs for mean 27 months (range 1-67 months). In this public cation, the mean time of follow-up was 29 months (range 7-74 months). **Source of funding** Bayer, National Starch and Chemical, UK Medical Research Council, Cancer Research UK, European Union, Cancer Council Victoria (Australia), The Technology and Human	Europe, 30% UK, 14% Australia and Hong Kong, 6% Southern Europe, 5% South Africa, 0.4% Americas **Inclusion criteria** Older than 25 years of age, proven carriers of a pathologic mismatch-repair mutation ("genetic diagnosis") 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 (clinical diagnosis'). Colonoscopic examination and clearance of polyps within 3 months after recruitment were prerequisites. If a partial colectomy had been performed, a daily bowel movement of three or fewer formed stools was required.	the placebo only, starch+placebo and the placebo+placebo groups combined into the *placebo group.* Participants in the resistant starch only group (N=41) were not included in this analysis.	colorectal cancer, other cancers associated with Lynch syndrome. (A neoplasm was classified as an advanced adenoma on the basis of one or more of the following features: a diameter of 1 cm or more, a villous or tubuvillous component, or high-grade dysplasia. Statistical analysis - Time-to-event analysis was used (Cox proportional HRs (adjusted for age and sex). Participants who withdrew from the study before the colonoscopic examination post-intervention were excluded from analysis, thus, per protocol analysis was done.	Development of adenoma and colorectal cancer at mean 29 months of follow-up Placebo: 3/343 Aspirin: 5/350 Development of advanced adenoma or colorectal cancer at mean 29 months of follow-up Placebo: 34/343 Aspirin: 26/350 Crude HR 0.9 95% CI 0.5 to 1.5 Adjusted HR 0.9 95% CI 0.5 to 1.5 (adjusted for number of colonoscopic examinations)	as adenoma or colorectal cancer whereas in the trial protocol they are listed separately).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Resources for Industry Programme (South Africa), Finnish Cancer Foundation.	**Exclusion criteria** Pregnancy, contraindications for the use of aspirin, the use of anti-inflammatory agents, severe intercurrent disease. Patients with recent bowel cancer were excluded for 1 year if the pathological findings were consistent with Dukes' stage A, for 2 years if they were consistent with Dukes' stage B, and for 5 years if they were consistent with Dukes' stage C or D.				
Full citation Burn, J, Gerdes, Am, Macrae, F, Mecklin, Jp, Moeslein, G, Olschwang, S, Eccles, D, Evans, Dg, Maher, Er, Bertario, L, Bisgaard, Ml, Dunlop, Mg, Ho, Jw, Hodgson, Sv, Lindblom, A, Lubinski, J, Morrison, Pj, Murday, V, Ramesar, R, Side, L, Scott, Rj, Thomas, Hj, Vasen, Hf, Barker, G, Crawford, G, Elliott, F, Movahedi, M, Pylvanainen, K, Wijnen, Jt, Fodde, R, Lynch, Ht, Mathers, Jc, Bishop, Dt, Long-term effect of	**Sample size** N=1071 participants allocated randomisation number. N=937 commenced intervention N=434 allocated to aspirin placebo N=427 allocated to aspirin **Characteristics** Demographic characteristics not reported in this publication (see evidence table for	**Interventions** Aspirin 600 milligram per day versus placebo. The trial also included intervention to give resistant starch or placebo, therefore, participants were randomly assigned to either aspirin+placebo, aspirin+starch, starch+placebo, or placebo+placebo but in this analysis only participants receiving aspirin and placebo with or without starch	**Details** Randomisation - Randomisation was computer-generated. It was done in blocks of 16 separately for six geographical groups of participating centres to ensure balance across the intervention arms. Allocation concealment Not reported. Blinding - The participants and the investigators were blinded for the study group allocations. Follow-up –	**Results** Development of colorectal cancer at mean 55.7 months of follow-up Placebo: 30/434 Aspirin: 18/427 Intention-to-treat (ITT) analysis: Placebo: reference Aspirin: HR 0.63 95% CI 0.35 to 1.13 and IRR 0.56 95% CI 0.32 to 0.99 Per protocol analysis: Placebo for 2 or more years: reference	**Limitations -** Cochrane risk of bias tool Selection bias Random sequence generation: low risk Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: low risk Detection bias Blinding of outcome assessment: low risk Attrition bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial, Lancet, 378, 2081-2087, 2011 **Ref Id** 702418 **Country/ies where the study was carried out** Australia, Denmark, Finland, France, Germany, Hong Kong, Italy, Netherlands, Poland, South Africa, Sweden, UK, US **Study type** RCT (CAPP2 trial, ISRCTN59521990) **Aim of the study** To "… investigate the antineoplastic effects of aspirin and a resistant starch in carriers of Lynch syndrome." **Study dates** Intervention was started by participants between January 1999 and March 2005. Intervention lasted for mean 29 months and the study had a pre-planned follow-up of 10	Burn et al. 2008 for more details about participant characteristics in this trial) but "… demographic data show no differences between those traced and not traced in this follow-up analysis with respect to age, sex, randomisation category, or geographical location. **Inclusion criteria** (From Burn et al. 2008) Older than 25 years of age, proven carriers of a pathologic mismatch-repair mutation ("genetic diagnosis") 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 ('clinical diagnosis'). Colonoscopic examination and clearance of polyps within 3 months after recruitment were	is considered. The participants had an option to be allocated to a single intervention only.	Primary outcome: development of colorectal cancer Secondary outcomes: development of colorectal adenomas or the development of other Lynch syndrome-related cancers, or both. Data on primary and secondary outcomes were collected at colonoscopic examination after 2 years of the intervention along with routine surveillance. Data on adverse events and compliance during the intervention was also collected. Data on adverse events post-intervention was not collected. Statistical analysis Analyses undertaken on ITT basis and per protocol. Time-to-event analysis (Cox-proportional hazard models) was conducted to estimate the hazard ratios (HRs) with 95% CIs (adjusted	Aspirin for 2 or more years: HR 0.41 95% CI 0.19 to 0.86 and IRR 0.37 95% CI 0.18 to 0.78 Aspirin for less than 2 years: HR 1.07 95% CI 0.47 to 2.41 and IRR 0.90 95% CI 0.42 to 1.91 Non-colorectal Lynch syndrome-related cancers at mean 55.7 months of follow-up Placebo: 22/434 Aspirin: 16/427 ITT analysis: Placebo: reference Aspirin: HR 0.63 95% CI 0.34 to 1.19 and IRR 0.63 95% CI 0.34 to 1.16 Per protocol analysis: Placebo for 2 or more years: reference Aspirin for 2 or more years: HR 0.47 95% CI 0.21 to 1.06 and IRR 0.49 95% CI 0.23 to 1.05 Aspirin for less than 2 years: HR 1.11 95% CI 0.46 to 2.68 and IRR 0.90 95% CI 0.38 to 2.14	Incomplete outcome data: high risk (Around 20% of the randomised were not included in the analysis and around 37% of the randomised had no long-term follow-up data. Per-protocol analyses performed for some comparisons/outcomes.) Reporting bias Selective reporting: unclear risk of bias (the secondary outcomes reported in the paper are different to the secondary outcomes listed in the trial protocol. In addition, both ITT and per-protocol analyses performed and reported, also both HRs and IRRs reported.) Other bias Other sources of bias: Data on adverse events were only collected during the intervention period and not during follow-up.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
years. The earliest recruited patients had reached 10 years of follow-up at the time of this analysis, the mean follow-up time was 55.7 months (range 1-128 months). **Source of funding** Funding initially provided by a European Union award supplemented by Programme funding in Newcastle and Leeds from Cancer Research UK. Bayer Corporation and National Starch and Chemical company provided free intervention including packaging and provided a donation to cover the costs of administration and distribution. (Bayer Corporation and National Starch and Chemical company had no influence on the study design, conduct or analyses or preparation of the manuscript.) The UK Medical Research Council was the primary funder. Financial contributions were also made by Newcastle Hospitals trustees,	prerequisites. If a partial colectomy had been performed, a daily bowel movement of three or fewer formed stools was required. Exclusion criteria (From Burn et al. 2008) Pregnancy, contraindications for the use of aspirin, the use of anti-inflammatory agents, severe intercurrent disease. Patients with recent bowel cancer were excluded for 1 year if the pathological findings were consistent with Dukes' stage A, for 2 years if they were consistent with Dukes' stage B, and for 5 years if they were consistent with Dukes' stage C or D.		for sex) of the effect of aspirin to develop colorectal cancer. Incidence rate ratios (IRRs) (adjusted for sex) were also calculated (Poisson regression) to estimate the effect of aspirin to develop potentially multiple primary cancers (total number of primary cancers, not just time to first cancer).	All Lynch-syndrome cancers at mean 55.7 months of follow-up Placebo: 52/434 Aspirin: 34/427 ITT analysis: Placebo: reference Aspirin: HR 0.65 95% CI 0.42 to 1.00 and IRR 0.59 95% CI 0.39 to 0.90 Per protocol analysis: Placebo for 2 or more years: reference Aspirin for 2 or more years: HR 0.45 95% CI 0.26 to 0.79 and IRR 0.42 95% CI 0.25 to 0.72 Aspirin for less than 2 years: HR 1.13 95% CI 0.62 to 2.06 and IRR 0.90 95% CI 0.51 to 1.59 Cerebral haemorrhage Placebo: 0/434 Aspirin: 0/427 Gastrointestinal bleed Placebo: 1/434 Aspirin: 1/427 Gastric ulcer Placebo: 1/434 Aspirin: 0/427 Duodenal ulcer	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cancer Council of Victoria Australia, THRIPP South Africa, The Finnish Cancer Foundation, SIAK Switzerland, Bayer Schering Pharma.				Placebo: 3/434 Aspirin: 3/427 Probable or possible peptic ulcer Placebo: 8/434 Aspirin: 7/427 Serious adverse event Placebo: 24/434 Aspirin: 21/427	
Full citation Ouakrim, D. A., Dashti, S. G., Chau, R., Buchanan, D. D., Clendenning, M., Rosty, C., Winship, I. M., Young, J. P., Giles, G. G., Leggett, B., Macrae, F. A., Ahnen, D. J., Casey, G., Gallinger, S., Haile, R. W., Le Marchand, L., Thibodeau, S. N., Lindor, N. M., Newcomb, P. A., Potter, J. D., Baron, J. A., Hopper, J. L., Jenkins, M. A., Win, A. K., Aspirin, Ibuprofen, and the Risk for Colorectal Cancer in Lynch Syndrome, Journal of the National Cancer Institute, 107, 2015 **Ref Id** 702783	**Sample size** N=2003 carriers of mismatch repair gene (MMR) mutation identified. N=1858 included in analyses. **Characteristics** Ethnicity: 93.4% white, 5.2% other, 1.2% missing Age, mean (SD): 41.7 years (12.2) Age, median (range): 42 years (18-85) Sex: 44.1% men, 55.8% women MMR mutation: 36.6% MLH1, 46.9% MSH2, 10.9% MSH6, 5.3% PMS2 Diabetes: 96.2% no Cigarette smoking: 51% never, 22.1% former, 26.5% current	**Interventions** Use of aspirin (the study also included the use of ibuprofen) Use of aspirin relevant for this study was defined as answering "yes" to "Have you ever taken aspirin at least twice a week for a month or longer?" 'Never use' was defined as answering "no" to "Have you ever taken aspirin at least twice a week for a month or longer?" Duration of aspirin use was based on the question "How long, in total, have you taken this medication for at least twice a week for a month or longer?"	**Details** Randomisation - Not a randomised study. Allocation concealment - Not applicable. Blinding - Not applicable. Follow-up - The information about the use of aspirin or ibuprofen and other medications, and personal and family history of cancer, history of cancer screening and history of polyps, polypectomy and other surgeries were collected using in-person interviews, telephone interviews, or mailed questionnaires. Reported cancer diagnoses and ages at diagnosis were confirmed if possible	**Results** Colorectal cancer Never user: reference (622/1572) Aspirin-only user: adjusted HR* 0.43 95% CI 0.25 to 0.75, p=0.003 (48/117) Aspirin-only user for between 1 month to 4.9 years: adjusted HR* 0.49 95% CI 0.27 to 0.90, p=0.02 (38/96) Aspirin-only user for 5 or more years: adjusted HR* 0.25 95% CI 0.10 to 0.62, p=0.003 (10/21) *Adjusted for year of birth, average lifetime alcohol intake and stratified by sex, country, cigarette smoking status, regular physical	**Limitations -** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias due to confounding (There is potential for confounding, for example age, but age has been accounted for in the analysis.) Bias in selection of participants into the study: Moderate risk of selection bias (There are obvious risks for selection bias because the groups with or without exposure (aspirin intake) are likely not similar although the characteristics of the two groups are not clearly reported in the paper. However, the analysis account for many characteristics such as age,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Australia, Canada, New Zealand, US **Study type:** Retrospective cohort. **Aim of the study:** To "… determine whether use of aspirin and ibuprofen in a nontrial setting is associated with the risk of colorectal cancer risk for MMR gene mutation carriers." **Study dates:** Recruitment and observation between 1997 and 2012. Source of funding National Cancer Institute, National Institutes of Health, Centre for Research Excellence, National Health and Medical Research Council (Australia).	**Inclusion criteria** Participants in the Colon Cancer Family Registry who have been genetically tested and found to be carriers of germline pathogenic mutation in an MMR gene. **Exclusion criteria** Not reported.	The age at first use of aspirin was calculated by subtracting the reported duration of use from the age at interview (with the assumption that duration of use was continuous and recent). The years between age at first use and the age at colorectal cancer diagnosis or censoring made up the total number of years of aspirin use. Those who answered "yes" to "Have you ever taken aspirin at least twice a week for a month or longer?" but reported a duration of use that was shorter than the time between age at interview and age at colorectal cancer diagnosis or censoring were classified as never users.	using pathology reports, medical records, cancer registry reports, and death certificates. Statistical analysis Cox proportional hazards regression was conducted. HRs with 95% CIs were calculated. Multivariable model included covariates based on statistical significance at the 25% level in the univariate models and on clinical importance for any variables not selected with this criterion. The following factors were considered potential confounders: year of birth, sex, country of recruitment, ethnicity, education, smoking status, and number of alcohol drinks per day, BMI 2 years before interview, history of diabetes, multivitamin supplement use, regular physical activity, acetaminophen, laxatives, hormone replacement therapy (women), and number	activity, and multivitamin intake.	alcohol intake, cigarette smoking etc.) At intervention Bias in classification of interventions: Serious risk of bias (There is serious concern of recall bias in relation to aspirin intake.) Post-intervention Bias due to deviations from intended interventions: Moderate risk of bias (Because of the retrospective nature and reliance on participant-recall, there are possible deviations from the "intended" interventions. Bias due to missing data: Low risk of bias due Bias in measurement of outcomes: Low risk of bias (Even though the measurement of outcomes is primarily based on participant-recall it is likely that the outcome is correctly measured because of the nature and severity of the outcome for the participant (colorectal cancer diagnosis).) Bias in selection of the reported result: Low risk of bias.

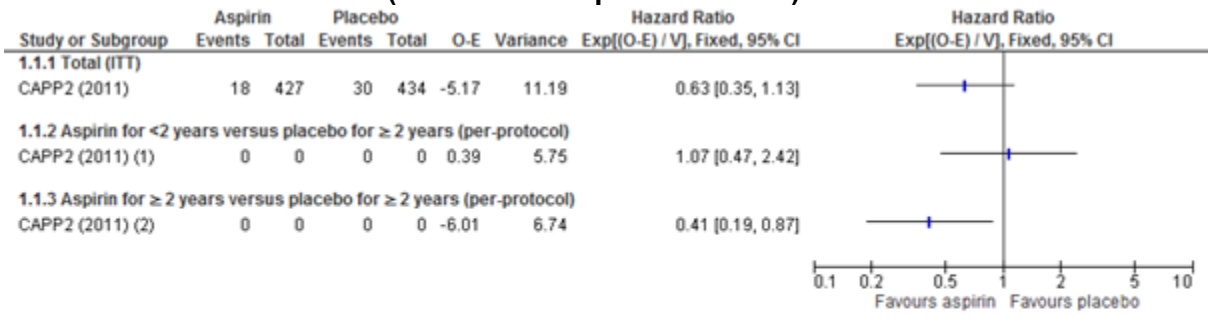
Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			of live births (women). Time at risk started at birth and ended at age at first diagnosis of colorectal or non-colorectal cancer, polypectomy (because removal of polyps lowers the colorectal cancer risk), or age at interview, whichever occurred first.		

BMI: body mass index; CI: confidence interval; HR: hazard ratio; IRR: incidence rate ratio; ITT: intention to treat; MMR: mismatch repair gene; N: number; RCT: randomised controlled trial; ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions; SD: standard deviation

1 Appendix E – Forest plots

2 Forest plots for review question: What is the effectiveness of aspirin in the 3 prevention of colorectal cancer in people with Lynch syndrome?

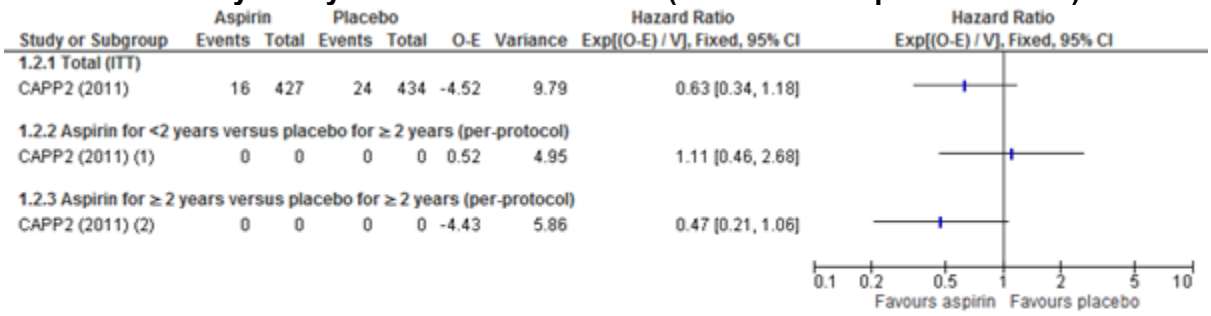
Figure 2: Aspirin versus placebo in people with Lynch syndrome – Development of colorectal cancer (mean follow-up 55.7 months)



Footnotes
(1) Number of events and total number of participants in each arm not reported.
(2) Number of events and total number of participants in each arm not reported.

CI: confidence interval; ITT: intention-to-treat; O-E: observed minus expected; V: variance

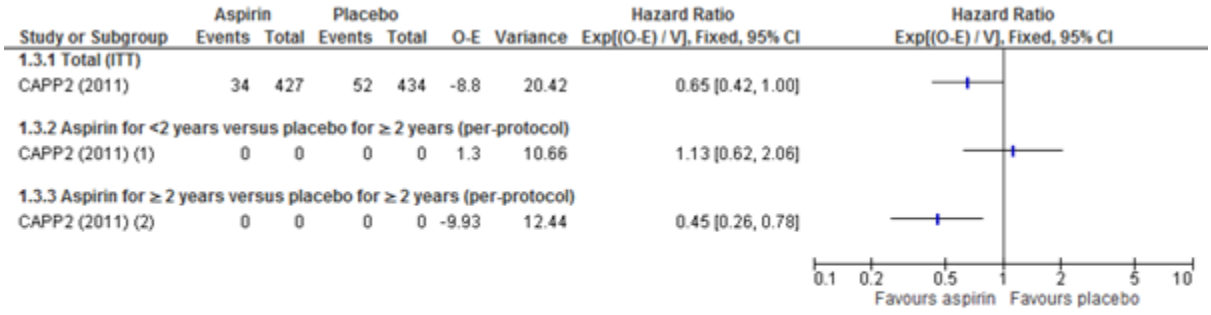
Figure 3: Aspirin versus placebo in people with Lynch syndrome – Development of non-colorectal Lynch syndrome-related cancer (mean follow-up 55.7 months)



Footnotes
(1) Number of events and total number of participants in each arm not reported.
(2) Number of events and total number of participants in each arm not reported.

CI: confidence interval; ITT: intention-to-treat; O-E: observed minus expected; V: variance

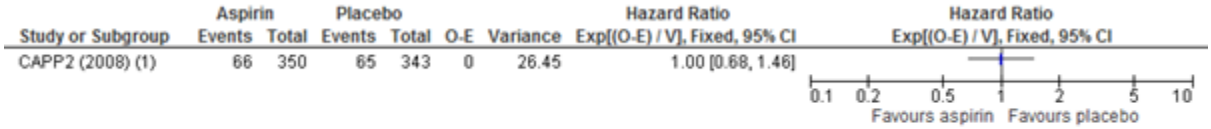
Figure 4: Aspirin versus placebo in people with Lynch syndrome – Development of any Lynch syndrome-related cancer (mean follow-up 55.7 months)



Footnotes
(1) Number of events and total number of participants in each arm not reported.
(2) Number of events and total number of participants in each arm not reported.

CI: confidence interval; ITT: intention-to-treat; O-E: observed minus expected; V: variance

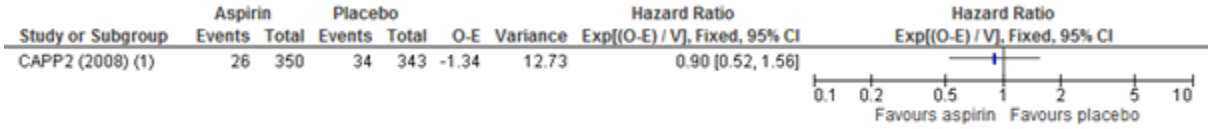
Figure 5: Aspirin versus placebo in people with Lynch syndrome – Development of adenoma or colorectal cancer (mean follow-up 29 months)



Footnotes
(1) Adjusted for the number of colonoscopic examinations.

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

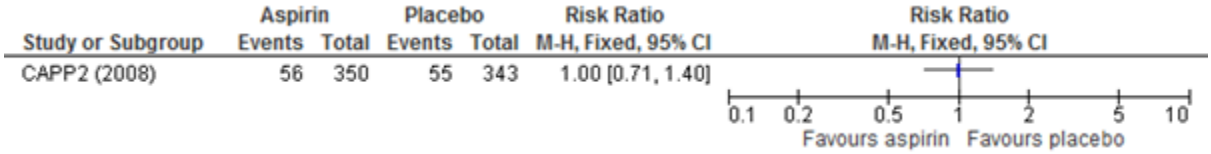
Figure 6: Aspirin versus placebo in people with Lynch syndrome – Development of advanced adenoma or colorectal cancer (mean follow-up 29 months)



Footnotes
(1) Adjusted for the number of colonoscopic examinations.

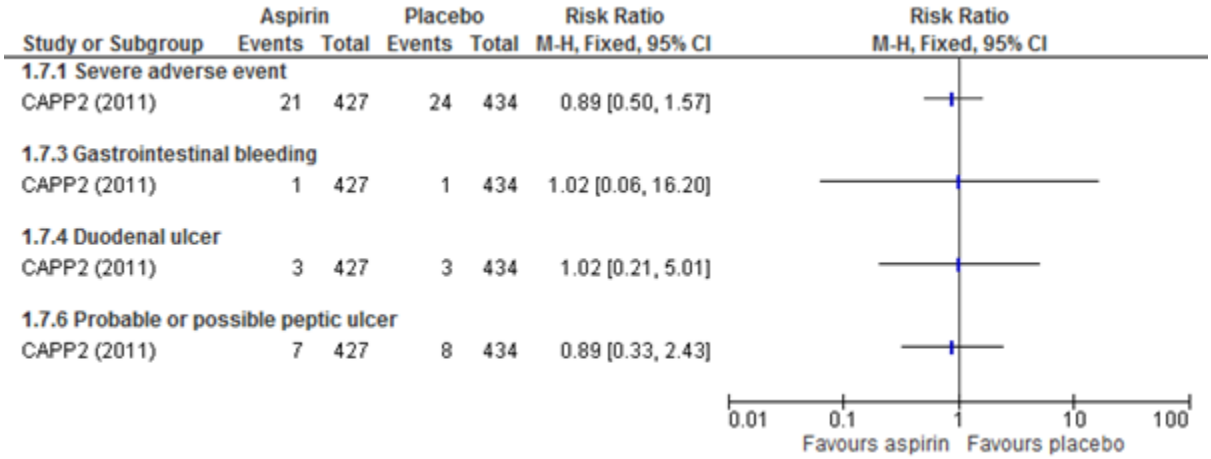
CI: confidence interval; O-E: observed minus expected; V: variance

Figure 7: Aspirin versus placebo in people with Lynch syndrome – Development of adenoma only (mean follow-up 29 months)



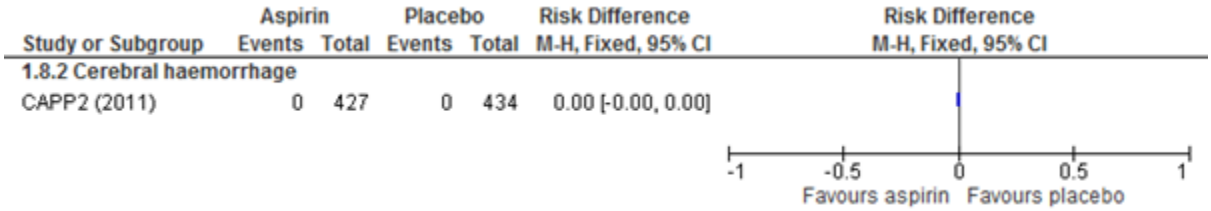
CI: confidence interval; O-E: observed minus expected; V: variance

Figure 8: Aspirin versus placebo in people with Lynch syndrome – Adverse events (during intervention) – severe adverse events, gastrointestinal bleeding, duodenal ulcer, probable or possible peptic ulcer



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

Figure 9: Aspirin versus placebo in people with Lynch syndrome – Adverse events (during intervention) – cerebral haemorrhage

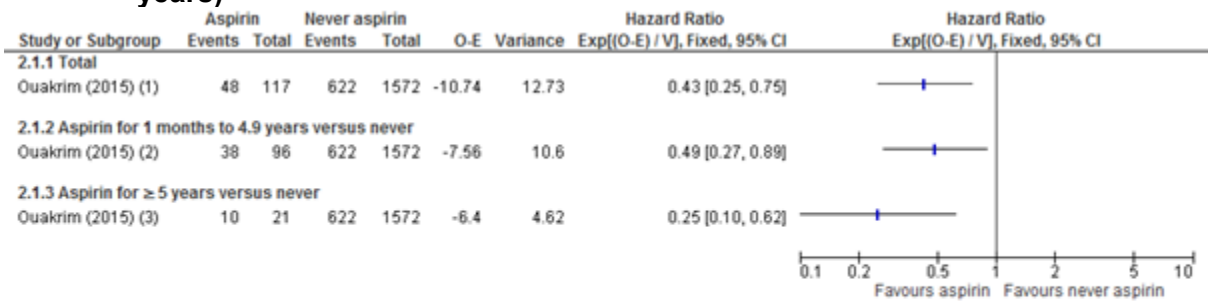


CI: confidence interval; M-H: Mantel-Haenszel

Figure 10: Aspirin versus placebo in people with Lynch syndrome – Adverse events (during intervention) – gastric ulcer

CI: confidence interval

Figure 11: Aspirin versus never aspirin in people with Lynch syndrome – Development of colorectal cancer at median age 42 years (range 18-85 years)



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

Appendix F – GRADE tables

GRADE tables for review question: What is the effectiveness of aspirin in the prevention of colorectal cancer in people with Lynch syndrome?

Table 5: Clinical evidence profile for comparison aspirin versus placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Overall survival												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Colorectal cancer - Total (ITT) (follow-up mean 55.7 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	18/427 (4.2%)	30/434 (6.9%)	HR 0.63 (0.35 to 1.13)	Placebo 5.7% at 5 years, aspirin 3.6% at 5 years (2.0% to 6.4%)	MODERATE	CRITICAL
Colorectal cancer - Aspirin for <2 years versus placebo for ≥2 years (per-protocol) (follow-up mean 55.7 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	NR	NR	HR 1.07 (0.47 to 2.42)	Placebo 5.6% at 5 years, aspirin 5.9% at 5 years (2.7% to 12.9%)	LOW	CRITICAL
Colorectal cancer - Aspirin for ≥2 years versus placebo for ≥2 years (per-protocol) (follow-up mean 55.7 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	NR	NR	HR 0.41 (0.19 to 0.87)	Placebo 5.6% at 5 years, aspirin 2.3% at 5 years	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Placebo	Relative (95% CI)	Absolute		
										(1.1% to 4.9%)		
Development of non-colorectal Lynch syndrome-related cancer - Total (ITT) (follow-up mean 55.7 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	16/427 (3.7%)	24/434 (5.5%)	HR 0.63 (0.34 to 1.18)	Placebo 5.0% at 5 years[3], aspirin 3.2% at 5 years (1.7% to 5.9%)	MODERATE	CRITICAL
Non-colorectal Lynch syndrome-related cancer - Aspirin for <2 years versus placebo for ≥2 years (per-protocol) (follow-up mean 55.7 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	NR	NR	HR 1.11 (0.46 to 2.68)	Placebo 5.0% at 5 years[4], aspirin 5.5% at 5 years (2.3% to 12.8%)	LOW	CRITICAL
Non-colorectal Lynch syndrome-related cancer - Aspirin for ≥2 years versus placebo for ≥2 years (per-protocol) (follow-up mean 55.7 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	NR	NR	HR 0.47 (0.21 to 1.06)	Placebo 5.0% at 5 years[4], aspirin 2.4% at 5 years (1.1% to 5.3%)	LOW	CRITICAL
Any Lynch syndrome cancer - Total (ITT) (follow-up mean 55.7 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	34/427 (8%)	52/434 (12%)	HR 0.65 (0.42 to 1)	Placebo 10.6% at 5 years, aspirin 7.0% at 5	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Placebo	Relative (95% CI)	Absolute		
										years (4.6% to 10.6%)		
Any Lynch syndrome cancer - Aspirin for <2 years versus placebo for ≥2 years (per-protocol) (follow-up mean 55.7 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	NR	NR	HR 1.13 (0.62 to 2.06)	Placebo 10.6% at 5 years[4], aspirin 11.9% at 5 years (6.7% to 20.6%)	LOW	CRITICAL
Any Lynch syndrome cancer - Aspirin for ≥2 years versus placebo for ≥2 years (per-protocol) (follow-up mean 55.7 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	NR	NR	HR 0.45 (0.26 to 0.78)	Placebo 10.6% at 5 years[4], aspirin 4.9% at 5 years (2.9% to 8.5%)	LOW	CRITICAL
Adenoma or colorectal cancer (follow-up mean 29 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	66/350 (18.9%)	65/343 (19%)	HR 1.00 (0.68 to 1.46)	Placebo 26.2% at 3 years, aspirin 28.4% at 3 years (21.5% to 36.7%)	LOW	IMPORTANT
Advanced adenoma or colorectal cancer (follow-up mean 29 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	26/350 (7.4%)	34/343 (9.9%)	HR 0.90 (0.52 to 1.56)	Placebo 14.5% at 3 years, aspirin 13.2% at 3 years (7.8% to 21.7%)	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Placebo	Relative (95% CI)	Absolute		
Adenoma only (follow-up mean 29 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	56/350 (16%)	55/343 (16%)	RR 1.00 (0.71 to 1.4)	0 fewer per 1000 (from 47 fewer to 64 more)	LOW	IMPORTANT
Adverse events (during intervention) - Severe adverse event												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[1]	none	21/427 (4.9%)	24/434 (5.5%)	RR 0.89 (0.5 to 1.57)	6 fewer per 1000 (from 28 fewer to 32 more)	LOW	IMPORTANT
Adverse events (during intervention) - Gastrointestinal bleeding												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[1]	none	1/427 (0.23%)	1/434 (0.23%)	RR 1.02 (0.06 to 16.2)	0 more per 1000 (from 2 fewer to 35 more)	LOW	IMPORTANT
Adverse events (during intervention) - Duodenal ulcer												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[1]	none	3/427 (0.7%)	3/434 (0.69%)	RR 1.02 (0.21 to 5.01)	0 more per 1000 (from 5 fewer to 28 more)	LOW	IMPORTANT
Adverse events (during intervention) - Probable or possible peptic ulcer												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[1]	none	7/427 (1.6%)	8/434 (1.8%)	RR 0.89 (0.33 to 2.43)	2 fewer per 1000 (from 12 fewer to 26 more)	LOW	IMPORTANT
Adverse events (during intervention) - Cerebral haemorrhage												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[1]	none	0/427 (0%)	0/434 (0%)	Not estimable	Not estimable	LOW	IMPORTANT
Adverse events (during intervention) - Gastric ulcer												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Placebo	Relative (95% CI)	Absolute		
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[1]	none	0/427 (0%)	1/434 (0.23%)	OR 0.14 (0.00 to 6.93)	2 fewer per 1000 (from 2 fewer to 17 more)	LOW	IMPORTANT

CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; NR: not reported; OR: odds ratio; RR: relative risk

1 The quality of evidence was downgraded by 1 because of imprecision of the effect estimate (less than 300 events).
2 The quality of evidence was downgraded by 1 because per-protocol analysis was performed and allocation concealment was not reported.
3 Estimated by subtracting the % of participants in the placebo group having had colorectal cancer at 5 years from the % of participants in the placebo group having had any Lynch syndrome-related cancer at 5 years.
4 Estimated to be similar to the % of participants in the overall placebo group.
5 The quality of evidence was downgraded by 1 because the data on adverse events was only collected during intervention period, allocation concealment was not reported.

Table 6: Clinical evidence profile for comparison aspirin versus never aspirin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Never aspirin	Relative (95% CI)	Absolute		
Overall survival												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Colorectal cancer - Total												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	48/117 (41%)	622/1572 (39.6%)	HR 0.43 (0.25 to 0.75)	Not estimable[3]	LOW	CRITICAL
Colorectal cancer - Aspirin for 1 months to 4.9 years versus never												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	38/96 (39.6%)	622/1572 (39.6%)	HR 0.49 (0.27 to 0.89)	Not estimable[3]	LOW	CRITICAL
Colorectal cancer - Aspirin for ≥5 years versus never												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aspirin**	**Never aspirin**	**Relative (95% CI)**	**Absolute**		
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	dose response gradient[2]	10/21 (47.6%)	622/1572 (39.6%)	HR 0.25 (0.1 to 0.62)	Not estimable[3]	LOW	CRITICAL
Development of non-colorectal Lynch syndrome-related cancers												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Development of colorectal adenomas												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Adverse events												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

1 *CI: confidence interval; HR: hazard ratio*
2 *1 The quality of evidence was downgraded by 1 because of high risk of recall bias regarding aspirin intake.*
3 *2 The quality of evidence was upgraded by 1 because of dose response gradient: longer duration of aspirin intake has a larger effect size than shorter duration of aspirin intake.*
4 *3 Not estimable because required data not reported.*

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the effectiveness of aspirin in the prevention of colorectal cancer in people with Lynch syndrome?

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 effectiveness of aspirin in the prevention of colorectal cancer in people with Lynch syndrome?

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the effectiveness of aspirin in the prevention of colorectal cancer in people with Lynch syndrome?

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic evidence analysis for review question: What is the effectiveness of aspirin in the prevention of colorectal cancer in people with Lynch syndrome?

No economic analysis was conducted for this review question.

1 Appendix K – Excluded studies

2 Excluded clinical studies for review question: What is the effectiveness of aspirin 3 in the prevention of colorectal cancer in people with Lynch syndrome?

4 **Table 7: Excluded studies and reasons for their exclusion**

Study	Reason for exclusion
Barton, M. K., Daily aspirin reduces colorectal cancer incidence in patients with Lynch syndrome, CA Cancer Journal for Clinicians, 62, 143-144, 2012	This publication summarises and reports the findings from the CAPP2 trial which is already included in this review.
Bishop, D. T., Burn, J., Mathers, J. C., Effect of Aspirin or Resistant Starch on Colorectal Neoplasia in the Lynch Syndrome *The authors reply*, New England Journal of Medicine, 360, 1462-1463, 2009	Authors' reply to letters to the editor.
Burn, J, Chapman, P, Mathers, J, Bulow, S, Mecklin, Jp, Bertario, L, Northover, J, Bishop, Dt, Vasen, H, Fodde, R, A randomised controlled trial of aspirin in prevention of colon cancer in carriers of mismatch repair gene defects; the CAPP2, International Journal of Colorectal Disease, 12, 173, 1997	The protocol for CAPP2 trial.
Burn, J, Mathers, Jc, Bishop, Dt, Chemoprevention in Lynch syndrome, Familial Cancer, 12, 707-718, 2013	This publication reports on the results of the CAPP2 trial which has already been included in the review (Burn et al. 2008, Burn et al., 2011), no additional relevant data reported.
Burn, J., Mathers, J., Bishop, D. T., Genetics, inheritance and strategies for prevention in populations at high risk of colorectal cancer (CRC), Prospects for Chemoprevention of Colorectal Neoplasia: Emerging Role of Anti-Inflammatory Drugs, Recent Results in Cancer Research. 191, 157-183, 2013	This publication re-reports the results of CAPP2 trial, no additional data.
Burn, J., Mathers, J., Bishop, D. T., Lynch syndrome: history, causes, diagnosis, treatment and prevention (CAPP2 trial), Digestive Diseases, 30 Suppl 2, 39-47, 2012	This publication summarises the findings from CAPP2 trial which were reported in more detail in other publications (Burn 2008 and Burn 2011).
Burn, J., Sheth, H., The role of aspirin in preventing colorectal cancer, British Medical Bulletin, 119, 17-24, 2016	A review, included studies checked for relevance.
Chan, A. T., Arber, N., Burn, J., Chia, W. K., Elwood, P., Hull, M. A., Logan, R. F., Rothwell, P. M., Schror, K., Baron, J. A., Aspirin in the chemoprevention of colorectal neoplasia: An overview, Cancer Prevention Research (Phila Pa), 5, 164-178, 2012	A review, included studies checked for relevance. The only relevant study mentioned is the CAPP2 trial which is already included in this review.
Chan, A. T., Lippman, S. M., Aspirin and colorectal cancer prevention in Lynch syndrome, Lancet, 378, 2051-2052, 2011	A comment, not a study.
Cooper, K., Squires, H., Carroll, C., Papaioannou, D., Booth, A., Logan, R., Maguire, C., Hind, D., Tappenden, P., Chemoprevention of colorectal cancer: Systematic review and economic evaluation, Health Technology Assessment, 14, 1-205, 2010	A systematic review and economic evaluation of chemoprevention of colorectal cancer. The only relevant data on aspirin as chemoprevention for people with Lynch syndrome from CAPP2 trial which is already included in this review.

DuPont, A W, Arguedas, M R, Wilcox, C M, Aspirin chemoprevention in patients with increased risk for colorectal cancer: a cost-effectiveness analysis (Provisional abstract), Alimentary Pharmacology and Therapeutics, 26, 431-441, 2007	Wrong population, no data among people with Lynch syndrome. Cost-effectiveness analysis.
Elwood, P. C., Almonte, M., Mustafa, M., Is there enough evidence for aspirin in high-risk groups?, Current Colorectal Cancer Reports, 9, 9-16, 2013	A narrative review. The only relevant reference is the CAPP2 trial which is already included in the review.
Garcia-Albeniz, X., Chan, A. T., Aspirin for the prevention of colorectal cancer, Best Practice and Research: Clinical Gastroenterology, 25, 461-472, 2011	A review, references checked. The only relevant study is the CAPP2 trial which is already included in this review.
Kanik, E. A., Canbaz, H., Colak, T., Aydin, S., Chemopreventive effect of nonsteroidal anti-inflammatory drugs on the development of a new colorectal polyp or adenoma in a high-risk population: A meta-analysis, Current Therapeutic Research - Clinical and Experimental, 65, 345-352, 2004	Wrong population, no data among people with Lynch syndrome.
Latchford, Andrew R, Maeda, Yasuko, Clark, Susan K, Nonsteroidal anti-inflammatory drugs (NSAID) and aspirin for preventing colorectal adenomas and carcinomas in patients with previous adenomas and/or genetic disposition, Cochrane Database of Systematic Reviews, 2013	A protocol for a Cochrane systematic review. No published systematic review has been found.
Lung, M. S., Trainer, A. H., Campbell, I., Lipton, L., Familial colorectal cancer, Internal Medicine Journal, 45, 482-491, 2015	A narrative review.
Lynch, P. M., Prevention of colorectal cancer in high-risk populations: The increasing role for endoscopy and chemoprevention in FAP and HNPCC, Digestion, 76, 68-76, 2007	A review from 2007. No relevant data presented.
Mathers, J. C., Movahedi, M., Macrae, F., Mecklin, J. P., Moeslein, G., Olschwang, S., Eccles, D., Evans, G., Maher, E. R., Bertario, L., Bisgaard, M. L., Dunlop, M., Ho, J. W., Hodgson, S., Lindblom, A., Lubinski, J., Morrison, P. J., Murday, V., Ramesar, R., Side, L., Scott, R. J., Thomas, H. J., Vasen, H., Gerdes, A. M., Barker, G., Crawford, G., Elliott, F., Pylvanainen, K., Wijnen, J., Fodde, R., Lynch, H., Bishop, D. T., Burn, J., Capp Investigators, Long-term effect of resistant starch on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial, Lancet Oncology, 13, 1242-9, 2012	Wrong intervention, no data on aspirin but on resistant starch.
Movahedi, M, Bishop, Dt, Macrae, F, Mecklin, Jp, Moeslein, G, Olschwang, S, Eccles, D, Evans, Dg, Maher, Er, Bertario, L, Bisgaard, Ml, Dunlop, Mg, Ho, Jw, Hodgson, Sv, Lindblom, A, Lubinski, J, Morrison, Pj, Murday, V, Ramesar, Rs, Side, L, Scott, Rj, Thomas, Hj, Vasen, Hf, Burn, J, Mathers, Jc, Obesity, Aspirin, and Risk of Colorectal Cancer in Carriers of Hereditary Colorectal Cancer: a Prospective Investigation in the CAPP2 Study, Journal of Clinical Oncology, 33, 3591-3597, 2015	This publication reports findings from CAPP2 trial stratified by BMI - not of interest according to the review protocol.
Nan, H., Hutter, C. M., Lin, Y., Jacobs, E. J., Ulrich, C. M., White, E., Baron, J. A., Berndt, S. I., Brenner, H., Butterbach, K., Caan, B. J., Campbell, P. T., Carlson, C. S., Casey, G., Chang-Claude, J., Chanock, S. J., Cotterchio, M., Duggan, D., Figueiredo, J. C., Fuchs, C. S., Giovannucci, E. L., Gong, J., Haile, R. W., Harrison, T. A., Hayes, R. B., Hoffmeister, M., Hopper, J. L., Hudson, T. J., Jenkins, M. A., Jiao, S., Lindor, N. M., Lemire, M., Le Marchand, L., Newcomb, P. A., Ogino, S., Pflugeisen, B. M., Potter, J. D., Qu, C., Rosse, S. A., Rudolph, A., Schoen, R. E., Schumacher, F. R., Seminara, D., Slattery, M.	Wrong population, no data among people with Lynch syndrome.

L., Thibodeau, S. N., Thomas, F., Thornquist, M., Warnick, G. S., Zanke, B. W., Gauderman, W. J., Peters, U., Hsu, L., Chan, A. T., Ccfr,, Gecco,, Association of aspirin and NSAID use with risk of colorectal cancer according to genetic variants, JAMA, 313, 1133-42, 2015	
Ruder, E. H., Laiyemo, A. O., Graubard, B. I., Hollenbeck, A. R., Schatzkin, A., Cross, A. J., Non-steroidal anti-inflammatory drugs and colorectal cancer risk in a large, prospective cohort, American Journal of Gastroenterology, 106, 1340-50, 2011	Wrong population, no data among people with Lynch syndrome.
Topping, D. L., Bird, A. R., Young, G. P., Effect of Aspirin or Resistant Starch on Colorectal Neoplasia in the Lynch Syndrome, New England Journal of Medicine, 360, 1462-1462, 2009	A letter to the editor.
Tsioulias, Gj, Go, Mf, Rigas, B, NSAIDs and Colorectal Cancer Control: Promise and Challenges, Current Pharmacology Reports, 1, 295-301, 2015	A review. References checked, no additional studies of relevance.
Wendling, P., Daily aspirin may prevent cancer in lynch syndrome, Oncology Report, 23, 2009	Not an original study, reporting findings from other studies.
Yang, F., Jin, C., Fu, D. L., Effect of Aspirin or Resistant Starch on Colorectal Neoplasia in the Lynch Syndrome, New England Journal of Medicine, 360, 1461-1462, 2009	A letter to the editor.

1

Appendix L – Research recommendations

Research recommendations for review question: What is the effectiveness of aspirin in the prevention of colorectal cancer in people with Lynch syndrome?

No research recommendations were made for this review question.