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Running head: RCT of a decision aid for cancer chemoprevention

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Abstract

Background

Australian guidelines recommend that all people aged 50-70 years old consider taking low-dose aspirin to reduce the risk of colorectal cancer (CRC).

Aim

To determine the effect of a consultation with a researcher before an appointment in general practice using a decision aid presenting the benefits and harms of taking low-dose aspirin on informed decision-making and low-dose aspirin use compared to a general CRC prevention brochure.

Design and Setting

Individually randomised controlled trial in six general practices in Victoria, Australia, from October 2020 to March 2021.

Method

Participants were recruited from a consecutive sample of patients aged 50-70 years attending a general practitioner (GP). The intervention was a consultation using a decision aid to discuss taking aspirin to reduce CRC risk; control consultations discussed reducing CRC risk generally. Self-reported co-primary outcomes were the proportion of individuals:1) making informed choices about taking aspirin at one month and 2) on low-dose aspirin uptake at six months, respectively. The intervention effect was estimated using a generalised linear model and reported with Bonferroni-adjusted 95% Confidence interval (CI) and p-values.

Results

261 participants (86% of eligible patients) were randomised into trial arms (129 intervention, 132 control). 17.7% (20/113) of intervention and 7.6% (9/118) control participants reported making an informed choice at one month, an estimated 9.1% (95% CI 0.29% to 18.5) between-arm difference in proportions [odds ratio (OR) 2.47 (97.5% CI:0.94 to 6.52) p=0.074]. The proportions of individuals self-reported who reported taking aspirin at six months was: 10.2% (12/118) intervention vs 13.8% (16/116) control (estimated between-arm difference: -4.0% (95% CI: -13.5 to 5.5); [OR= 0.68 (97.5% CI:0.27 to 1.70), p= 0.692].

Conclusion

The decision aid improved informed decision-making, but this did not translate into long-term regular use of aspirin to reduce CRC risk.

Keywords: General practice, Colorectal cancer, Aspirin, Guideline implementation, Decision Aid, Informed decision making, randomised controlled trial

How this fits in:

Australian guidelines recommend people aged 50 to 70 years take low-dose aspirin to prevent colorectal cancer (CRC). With the publication of these guidelines, there was no formal plan to implement them in clinical practice. This randomised controlled trial tested the use of a decision aid in general practice to communicate the benefits and harms of aspirin compared with general information on ways to prevent CRC. Additional implementation strategies with greater engagement with GPs may be necessary to increase aspirin use for CRC prevention.

Main text

1. Introduction

In 2020, colorectal cancer (CRC) was the second most common cause of cancer deaths in Australia, and there were an estimated 1.9 million cases diagnosed globally.[1,2] Meta-analyses of randomised controlled trials (RCTs) of low-dose aspirin have demonstrated reduced relative incidence and mortality of CRC by up to 25% and 33% respectively.[3] Meta-analyses of trials of aspirin for primary prevention of cardiovascular disease (CVD) demonstrate a reduced risk of ischaemic stroke, but an increased risk of non-fatal bleeding.[4] The side effects of aspirin are well defined [5], but the likelihood of preventing death from cancer is 5 to 10 times greater than causing death from taking aspirin in this age group.[6] These data informed Australian guidelines which recommend clinicians consider prescribing low-dose aspirin for people aged between 50 and 70 years to prevent CRC.[7]

Decision aids are effective in general practice for communicating the benefits and risks of an intervention [8], particularly for preference-sensitive decisions. Decision aids can support informed choices about aspirin by individuals with Lynch Syndrome [9] and could support this decision for the general population in primary care.

Should I Take Aspirin? (SITA) trial is an efficacy trial of a consultation in general practice using a novel decision aid demonstrating the potential harms and benefits of low-dose aspirin for CRC and CVD prevention on informed decision-making and low-dose aspirin uptake compared with general information about CRC.

2. Method

Brief methods are presented here, summarising the published trial protocol.[10]

2.1 Study design and setting

A phase II multi-site parallel two-arm individual RCT in six general practices in Victoria, Australia.

2.2 Participant inclusion and exclusion criteria

Participants were eligible if aged 50 -70 years, literate in written English, and provided informed consent. Exclusion criteria included those taking low-dose aspirin or an anticoagulant regularly, a previous diagnosis of CRC, a known genetic predisposition to CRC, or an extensive family history suggesting a genetic predisposition.[11] An extensive family history includes two or more first or second-degree relatives on the same side with CRC, or three or more first or second-degree relatives on the same side of the family with CRC or other Lynch Syndrome-related cancer. [11]

2.3 Recruitment

The practice provided researchers with appointment lists of patients who were in the eligible age range and had an appointment booked the following day to see if they might be interested in the SITA trial. Once contacted, if they were interested and eligible, the researcher invited them to attend a consultation in either a private consulting room at the general practice or using password-protected Zoom Videoconferencing with them before their planned GP consultation. Informed consent was obtained during the consultation, followed by baseline data collection, and randomisation, and depending on the trial arm, either the intervention or control protocol was delivered. Participants were informed that the trial was called '*The Bowel Cancer Prevention Study*' and were not explicitly told that it was about aspirin. After this, the patient had a consultation with their GP. Patients who refused or were ineligible were reassured that this would not be recorded in their medical records, and their clinical care would not be compromised.[12]

2.4 Intervention

The intervention involved a consultation delivered by a trained research assistant, in which the decision aid was discussed before the participant's scheduled GP appointment. The decision aid was a sex-specific, tri-fold brochure, which used expected frequency trees to present the absolute changes in risk in people taking daily low-dose aspirin on the incidence of CRC, stroke, myocardial infarction, gastrointestinal bleeding, and all-cause mortality. (Supplementary Figures 1 and 2)[10] The decision aid referred to the Cancer Council Australia guidelines, prompted participants to discuss their decision with their GP before commencing low-dose aspirin, and listed contraindications for aspirin use.[13] In response to the COVID pandemic, we developed an alternative teletrial model that involved a video version of the decision aid, [10] which was shown to all intervention participants.[14]

2.5 Control

The control arm involved a consultation before seeing their GP delivered by the same research assistants in which a 'Reduce your colorectal cancer risk' tri-fold control brochure with an accompanying video was presented (Supplementary Figure 3). The control brochure and video focused on modifiable risk factors and CRC screening with limited reference to low-dose aspirin.

2.6 Changes to the trial methods

There was a deviation to the published protocol. In the protocol, a short message service (SMS) was planned to be sent two weeks after randomisation to remind intervention participants to discuss taking aspirin with their

GP. However, at the end of the trial, we discovered the messages had not been automatically dispatched due to a technical issue and no one received an SMS.

2.7 Study outcomes and measures

Outcomes were measured at baseline before randomisation and at one and six months after randomisation. The one and six-month follow-up questionnaires sent to participants can be found in the SITA trial protocol paper supplementary files I and J.[10]

***2.7.1 The two co-primary outcomes were the difference between the study arms in*:**

a. Proportion of participants making an informed choice at one month

We used the multi-dimensional measure of informed choice (MMIC) to evaluate informed decision-making of participants regarding their self-reported behaviour of taking low-dose aspirin. [15] An informed choice was considered to be one where the individual has sufficient knowledge about taking aspirin to prevent CRC and CVD and where their behaviour (taking aspirin regularly in the past month or not) is concordant with their attitudes towards taking aspirin (positive or negative).[15] Sufficient knowledge was defined using a total score (range 0 to 1), which was the sum of 11 statements about aspirin for which the participant answered true, false, or unsure plus one open-ended item (Supplementary Box 1). The threshold for sufficient knowledge was a score of 8.2 determined using the Angoff method.[16] Attitude consists of four items on a seven-point Likert scale about taking aspirin.[15] The total attitude scores range from 4 to 28, with higher scores reflecting a more negative attitude. The cut-off for a positive or negative attitude was set at the mid-point of the scale (positive attitude: 4-15; negative attitude: 16-28)[15].

b. Proportion who self-reported daily adherence to low-dose aspirin at six months.

Participants were asked whether they had taken aspirin for at least five days per week, consistently, since consent (yes/no).

2.7.2 Secondary outcomes included the differences between the study arms in:

1) Mean Decisional Conflict scale at one month.[17]
2) Proportion who self-reported daily adherence to low-dose aspirin at one month.
3) Proportion of participants who discussed aspirin with their GP between baseline and six months, which was collected in an electronic medical record audit at 6 months by a research assistant blinded to participant allocation.

4) Proportion who reported behavioural changes made to reduce their risk of CRC at one and six months including dietary changes, quitting smoking, screening for CRC, and whether they spoke to their GP about these changes.

2.6.1 Baseline measures

Participant demographics and CRC and CVD risk factors were collected at baseline. Family history was used to evaluate CRC risk considering close relatives diagnosed with CRC before age 55 or multiple relatives diagnosed with CRC, indicating an elevated CRC risk, while self-reported risk factors including diabetes, high cholesterol, current use of high blood pressure medication, family history of CVD, and history of cigarette smoking indicated increased CVD risk for the participant.

Socio-economic status was based on the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD)[18] using the participant's postcode of residence. We used the SNS [19] to determine individuals' preferences for numerical versus prose information. SNS is an eight-item questionnaire, where each item is rated on a Likert scale to calculate the total score, and then the average score is calculated. A higher score indicates a higher preference for numerical information. We further collected the participants' age, sex, country of birth, number of medications they were taking, education, and language spoken at home.

2.8 Randomisation and blinding

Participants were randomly allocated 1:1 to the intervention or control arms using a computer-generated allocation sequence generated by the trial statistician and stratified by general practice, sex, and mode of intervention delivery (face-to-face or teletrial) using permuted blocks of random sizes of two and four within the stratum. GPs and research assistants who delivered the intervention and control could not be blinded but were not involved in the collection of follow-up data or data analysis. Before consenting, GPs were shown the decision aid and were made aware that their patients may ask about taking low-dose aspirin to prevent CRC. GPs were advised against changing their usual clinical practices during the trial.

Trial investigators were blinded to the participant allocation. Participants were blinded and advised that they would be randomly assigned to one of two groups and, in either, they would receive information about reducing their CRC risk.

2.9 Sample size

A total of 258 participants (129 per arm) were required to achieve 80% power with a two-sided Bonferroni-adjusted 2.5% alpha level for the two co-primary outcomes to estimate a minimum 20% between-arm

difference in the (a) proportion of participants regularly using low-dose aspirin at 6 months (39% vs 19%), and (b) proportion making an informed choice about low-dose aspirin use at 1 month (54% vs 34%). This allowed for 15% attrition at 6 months.

2.10 Statistical analysis

The detailed statistical analysis plan (SAP) is available on the Australian New Zealand Clinical Trials Registry (ANZCTR) ID: ACTRN12620001003965 [20] All analyses were conducted using STATA version 17.[21]

Descriptive statistics were used to compare baseline participant demographic characteristics between the two study arms. Analysis was intention to treat for the two co-primary and secondary outcomes 1 to 3, where all randomised participants were included in the analysis using a multiple imputation approach (See Supplementary 2 for details). Exceptions were participants who explicitly withdrew their data before data analysis. For binary outcomes, logistic regression, adjusted for general practice (metropolitan vs rural), brochure type based on sex (male vs female), and mode of trial delivery (face-to-face or tele-trial), was used to estimate the odds ratio (relative measure). Adjusted estimates of the between-arm difference in proportions (absolute measure) were generated using Stata margins command after fitting the logistic model.[22] We were unable to estimate the between-arm difference in proportions using the generalised linear model (GLM) with the identity link function and binomial family as originally planned due to model convergence issues for several binary outcomes. The between-arm difference in means for the decisional conflict scale was estimated using linear regression adjusted for general practice, brochure type, and delivery mode. In addition, we conducted three sensitivity analyses: (1) adjusted for pre-specified baseline variables, general practice, sex, and mode of delivery using the same regression models; (2) the same as 1 we adjusted for age in years and numeracy using the Subjective Numeracy Scale (SNS), and (3) participants with complete follow-up only. Estimates of the intervention effect were presented with Bonferroni-adjusted 95% confidence interval and p-values for two comparisons, for the co-primary outcomes and with 95% confidence intervals for all other secondary outcomes.

3. Results

3.1 Flow of participants in the trial and loss to follow-up

Between October 2020 and March 2021, 264 participants consented (87.1% of 303 eligible patients) from six general practices and were randomly allocated to the two trial arms. (Figure 1) Three participants allocated to the intervention were found to be taking anticoagulants, which for the purposes of this trial were considered as contraindicated with taking low-dose aspirin and were excluded from analyses. Survey response rates were high

at 85.6% and 89.2% at one and six months respectively. Participant characteristics in the two arms were similar, apart from a family history of CVD or CRC. (Table 1)

3.2 Co-primary outcomes

Nearly 18% of participants in the intervention arm who reported making an informed choice about taking low-dose aspirin compared to 7.6% in the control arm an estimated increase of 9.1% (Bonferroni-adjusted 95% CI 0.29 to 18.5; [odds ratio (OR) 2.47 (Bonferroni-adjusted 95% CI: 0.94 to 6.52) Bonferroni-adjusted p=0.074]). (Table 2) There was no statistical evidence to support a difference in the proportion of participants reporting daily use of low-dose aspirin at 6 was months between the intervention and control arms (10.2% vs 13.8%; between-arm difference of -4.0%; 95% CI: -13.5 to 5.5 OR= 0.68 [97.5% CI:0.27 to 1.70], p= 0.346). Similar results were observed in the sensitivity analyses. Over half the participants had insufficient knowledge about taking aspirin, had a negative attitude about aspirin and were not taking low-dose aspirin at 1 month (41.5% intervention and 60.1% control arm), forming the most common group of uninformed choices. (Table 3)

3.3 Secondary outcomes (Tables 2 and 4)

There was no statistical evidence to support between-arm differences in mean decisional conflict (Table 2). In the medical records audit, a higher proportion of intervention participants (17.5%) were identified as discussing taking aspirin with the GP compared to 9.0% of controls (between-arm difference 8.6%; (95% CI: -0.39% to 17.7%; OR=2.09 [95% CI:0.95 to 4.56], p=0.066) (Table 2). Similarly, there was strong evidence that a greater proportion of participants in the intervention arm (30%) reported discussing aspirin with their GP compared to control arm participants (15%) at the 1 and 6 months, respectively (Table 4). There was no statistical evidence to support between-arm differences in the proportion of participants for other self-reported behaviour change for other modifiable risk factors, that were included in the control brochure, except for self-reported discussion about screening for colorectal cancer at 1 month. (Table 4)

Discussion

This is the first trial assessing the efficacy of a decision aid to support discussions about low-dose aspirin to prevent CRC in an average-risk general practice population. There is a long history of aspirin being recommended to prevent CVD and stroke although most international guidelines now recommend this only for secondary prevention.[23–26] Meta-analyses of aspirin trials for CVD prevention and CRC informed the Australian CRC chemoprevention guidelines [7], but implementation plans were lacking. We developed the first sex-specific decision aids for low-dose aspirin use, as a potential route for clinical implementation of these guidelines.[27]

Our trial showed an increase in mean knowledge scores and informed decisions about taking low-dose aspirin to prevent CRC at one month, and a higher proportion of participants discussing taking aspirin in the intervention arm, but little impact on uptake in low-dose aspirin after six months. Most participants made an informed choice decided against taking low-dose aspirin, and the estimated between-arm difference of 9.1% in the proportion making an informed fell below the predetermined minimum threshold of 20%, which was considered clinically important by trial investigators.

Strengths and limitations

We randomised individuals as the risk of contamination was expected to be low based on similar trials [28] and the intervention was delivered at an individual level. Further, we would have required a larger sample size if the unit of randomisation was the practice. To minimise the risk of contamination in the control arm, the trial's focus on aspirin was concealed from all participants. However, the intervention effect may have been attenuated through multiple questionnaires about aspirin use to participants. GP involvement in the trial may have also raised awareness of aspirin guidelines and led them to discuss this with their patients. More than 15% of control participants reported a discussion about aspirin with their GP and, even though more participants in the intervention arm (30%) discussed taking low-dose aspirin with their GP, we do not know the content of those discussions, nor how GPs' attitudes towards aspirin may have influenced patients' decisions. There were fewer discussions about aspirin recorded in participants' medical records than self-reported by participants. This might be due to social desirability bias influencing participant self-reported responses, or the GP not referring to this conversation in their records.

Recruitment and retention rates of trial participants were high, achieved with the use of a novel teletrial and an adapted protocol for online trial delivery during the COVID-19 pandemic.[14] A limitation of the efficacy trial design was that we could not determine whether the use of our decision aid by a practice nurse or GP, rather than in a standardised way by a researcher, would result in increased low-dose aspirin use.

Most participants did not demonstrate sufficient knowledge to make an informed decision based on the MMIC measure. A limitation of the MMIC is the need to define a binary cut-point on the knowledge and attitude scales. We used the Angoff method in which a group of researchers and clinicians reached a consensus on the cut-point for sufficient knowledge. The cut-point for sufficient knowledge may have been set too high (higher than the midpoint for knowledge score) resulting in a lower proportion of participants classified as making informed choices. The MMIC was measured at one month to allow sufficient time to observe a behaviour change (taking aspirin). Intervention participants may have potentially reduced knowledge scores at 1 month, then if surveyed

immediately on receipt of the intervention, which may have attenuated the estimated intervention effect. Retained knowledge may be a more important measure of informed decision-making than short-term recall.

Comparison with existing literature

To date, only one decision aid about using aspirin for primary prevention of CRC has been evaluated and shown to be acceptable to GPs and pharmacists but its effectiveness on low-dose aspirin uptake and patient-informed choice has not been tested in a trial. [29] A systematic review of decision aids for complex healthcare decisions found that they increased knowledge, facilitated discussions between clinicians and patients, and reduced decisional conflict,[8] but their effect on informed decision-making was less consistent across trials. [8] In this trial, the proportion of intervention participants reporting making informed choices increased by 9.1% compared to the control participants, but the overall proportion making informed choices was low. Most participants had insufficient knowledge, leading them not to make informed choices about aspirin.

Implications for research and practice

This trial of a decision aid to implement aspirin guidelines to prevent CRC led to differences in knowledge, and informed choice and prompted discussions between patients and GPs while there was no difference in aspirin uptake between the study arms. Since the Australian guidelines recommending low-dose aspirin for CRC prevention were published, the ASPREE trial results have been published which cast doubt on the benefits of low-dose aspirin in primary prevention for many conditions in healthy Australians over 70 years of age.[30] Furthermore, the US Preventive Services Taskforce have modified its recommendations about the use of aspirin for CRC prevention.[31] Although the ASPREE trial involved an older population than the Australian guidelines recommend considering aspirin, the publicity and media coverage surrounding the ASPREE trial in Australia possibly created confusion for GPs and the general public at the time of this trial. The decision aid we trialled was designed to clarify the evidence on the relative benefits and harms of low-dose aspirin for primary prevention in people aged 50-70 years both for patients and their GPs. To implement the guidelines, other interventions in addition to decision aids might be needed to be tested. It may require GPs to be more confident in the strength of evidence underpinning the aspirin recommendations before they are comfortable supporting their patients in taking regular aspirin to prevent CRC and other long-term conditions.

Additional information

At the end of the text and before the references we ask authors to report:

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- Ethics: ethics approval was granted by the University of Melbourne Human Research Ethics Committee in 2020 (ID 2056513).
- Competing interests: JE, FM and MJ were members of the Cancer Council Australia guideline development group which recommends the use of low dose aspirin for the prevention of CRC. No other authors had any competing interests.

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Table 1. Descriptive statistics of baseline characteristics for all participants and by study arm.

	All participants % (n)	Intervention % (n)	Control % (n)
Total	261	129	132
Age (years), mean (SD)	60.8 (6.3)	60.8 (6.3)	60.9 (6.3)
Sex			
Female	59.8% (156)	59.7% (77)	59.8% (79)
Male	39.8% (107)	39.5% (51)	40.2% (53)
Transgender	0.4% (1)	0.8% (1)	0% (0)
Male or female decision aid			
Female	59.8% (156)	59.7% (77)	59.8% (79)
Male	40.2% (105)	40.3 (52)	40.2% (53)
IRSAD Socio-Economic status[1]			
Disadvantaged 1	3.8% (10)	5.4% (7)	2.3% (3)
2	2.3% (6)	0.8% (1)	3.8% (5)
3	37.5% (98)	41.1% (53)	34.1% (45)
4	16.3% (43)	13.2% (17)	19.7% (26)
Advantaged 5	39.8% (104)	39.5% (51)	40.2% (53)
Country of birth			
Australia	67.8% (177)	67.4% (87)	68.2% (90)
Overseas	32.2% (86)	32.6% (42)	31.8% (42)
Current medications, excluding vitamins			
None	31.0% (81)	28.7% (37)	33.3% (44)
One	22.2% (58)	21.7% (28)	22.7% (30)
Two to three	23.8% (62)	20.2% (26)	27.3% (36)
Four to five	13.0% (34)	15.5% (20)	10.6% (14)
More than five	10.0% (26)	14.0% (18)	6.8% (8)
Education			
Never completed high school	15.7% (41)	15.2% (20)	16.3% (21)
Completed high school only	18.8% (49)	16.7% (22)	20.9% (27)
TAFE qualifications or similar	21.1% (55)	25.0% (33)	17.1% (22)
University degree or higher	44.4% (116)	43.2% (57)	45.7% (59)
Languages spoken at home			
English	94.3% (246)	94.6% (122)	93.9% (124)
Other	5.7% (15)	5.4% (7)	6.1% (8)
Subjective numeracy score – mean (SD)	4.1 (1.2)	4.1 (1.3)	4.2 (1.1)

Notes: SD = Standard deviation. *The Index of Relative Socio-economic Advantage and Disadvantage (IRSAD)

Table 1. Continued

	All participants % (n)	Intervention % (n)	Control % (n)
Total	261	129	132
General practice			
Metropolitan clinic 1	12.0% (31)	11.6% (15)	12.1% (16)
Regional clinic 2	4.2% (11)	4.7% (6)	3.8% (5)
Regional clinic 3	26.8% (70)	27.1% (35)	26.5% (35)
Metropolitan clinic 4	26.8% (70)	25.6% (33)	28.0% (37)
Metropolitan clinic 5	15.3% (40)	16.3% (21)	14.4% (19)
Metropolitan clinic 6	14.9% (39)	14.7% (19)	15.2% (20)
Mode of trial delivery			
Teletrial	21.1% (55)	20.9% (27)	21.2% (28)
Face-to-face	78.9% (206)	79.1% (102)	78.8% (104)
Cardiovascular disease risks			
Family history of heart attack or stroke			
Yes	55.9% (146)	51.9% (67)	59.8% (79)
No	38.7% (103)	41.9% (54)	35.6% (47)
Unsure	5.4% (14)	6.2% (8)	4.5% (6)
Personal history of diabetes			
Yes	7.3% (19)	8.5% (11)	6.1% (8)
No	92.3% (241)	90.7% (117)	93.9% (124)
Unsure	0.4% (1)	0 (0%)	0 (0%)
Taking medication for high blood pressure			
Yes	26.8% (70)	29.5% (38)	24.2% (32)
No	72.8% (190)	69.8% (90)	75.8% (100)
Unsure	0.4% (1)	0.8% (1)	0% (0)
Personal history of high cholesterol			
Yes	39.5% (103)	39.5% (51)	39.4% (52)
No	58.2% (152)	59.7% (77)	56.8% (75)
Unsure	2.3% (6)	0.8% (1)	3.8% (5)
Current or history of smoking cigarettes	47.5% (124)	47.3% (61)	47.7% (63)
Family history of colorectal cancer[2]			
Yes	3.8% (10)	1.6% (2)	6.1% (8)
No	92.7% (241)	95.3% (122)	90.2% (119)
Unsure	3.5% (9)	3.1% (4)	3.8% (5)

SD = Standard deviation.

1 The Index of Relative Socio-economic Advantage and Disadvantage (IRSAD)

2 Participants were asked if they had more than one relative who had bowel cancer at any age, a family history of bowel cancer that did not meet the exclusion criteria for the trial

Table 2. Co-primary outcomes and secondary outcomes by study arm for the SITA trial (N=261).

	Intervention	Control	Estimated effect size		
Number of participants	129 (49.4%)	132 (50.6%)			
Co-primary Outcomes			**Difference (Bonferroni adjusted 95% CI)**	**Odds Ratio (Bonferroni adjusted 9%% CI)**	**Bonferroni adjusted p-value**
Self-reported daily aspirin at 6-months	10.2% (12/118)	13.8% (16/116)			
Primary analysis[1]			-4.0% (-13.5 to 5.5)	0.68 (0.27 to 1.70)	0.692
Sensitivity analysis [2]			-3.1 (-12.4 to 6.3)	0.74 (0.29 to 1.88)	0.932
Sensitivity analysis (n=234)[3]			-3.6% (-12.9 to 5.8)	0.70 (0.28 to 1.78)	0.790
Informed choice about taking aspirin at 1-month	17.7% (20/113)	7.6% (9/118)			
Primary analysis[1]			9.1% (0.29 to 18.5)	2.47 (0.94 to 6.52)	0.074
Sensitivity analysis [2]			9.6% (0.17 to 17.6)	2.70 (1.14 to 6.44)	0.048
Sensitivity analysis (n=231)[3]			9.9% (0.31 to 19.5)	2.63 (1.00 to 6.93)	0.050
Secondary Outcomes			**Difference (95% CI)**	**Odds Ratio (95% CI)**	**p-value**
Decisional conflict scale at 1 month- mean (SD)	28.0 (SD=16.4) n=114	31.7 (SD=18.8) n=123			
Primary analysis[4]			-3.54 (-7.87 to 0.79)		0.109
Sensitivity analysis [5]			-3.73 (-8.08 to 0.62)		0.093
Sensitivity analysis (n=237)[6]			-3.70 (-8.18 to 0.76)		0.104
Self-reported daily aspirin at 1-month	9.6% (11/115)	5.6% (7/125)			
Primary analysis[1]			3.7% (-3.6 to 11.0)	1.65 (0.61 to 4.45)	0.322
Sensitivity analysis [2]			3.9% (-2.8 to 10.6)	1.71 (0.63 to 4.60)	0.289
Sensitivity analysis (n=240)[3]			4.1% (-2.6 to 10.7)	1.83 (0.68 to 4.95)	0.233
GP record audit, spoke to GP about taking aspirin at six months (n=225)	17.5% (20/114)	9.0% (10/111)			

Primary analysis[1]	8.6% (-0.39 to 17.7)	2.09 (0.95 to 4.56)	0.066
Sensitivity analysis [2]	8.1% (-3.1 to 17.1)	2.60 (1.07 to 6.32)	0.035
Sensitivity analysis (n=225)[3]	8.3% (-0.38 to 17.0)	2.13 (0.94 to 4.82)	0.069

Notes: Difference, difference in percentages between arms; OR odds ratio; SD = Standard deviation; CI = Confidence interval.

1 Estimated using logistic regression adjusted for general practice, sex, and mode of delivery. Estimated using multiple imputation. Bonferroni adjusted 95% Confidence interval and p-values reported for co-primary outcomes.

2 Sensitivity analysis was same as 1, except also adjusted for age in years and numeracy scale; Estimated using multiple imputation.

3 Sensitivity analysis was same as 1 using only participants that completed follow-up

4 Estimated using linear regression adjusted for general practice, sex, and mode of delivery. Estimated using multiple imputation.

5 Sensitivity analysis was same as 4, except also adjusted for age and numeracy scale; Estimated using multiple imputation.

6 Sensitivity analysis was same as 4 using only participants who completed follow-up

Table 3. Informed and uninformed choices across the three domains of the multi-dimensional measure for informed choice (MMIC), at 1-month post-randomisation

		Sufficient knowledge	Attitude	Behaviour	Intervention (n= 113)	Control (n=118)	Total (n=231)
All possible informed choices							
	1	□	□	□	6 (5.3%)	3 (2.5%)	9 (3.9%)
	2	□	✗	✗	14 (12.4%)	6 (5.1%)	20 (8.7%)
All possible uninformed choices							
	3	□	✗	□	0 (0%)	0 (0%)	0 (0%)
	4	□	□	✗	16 (14.2%)	8 (6.8%)	24 (10.4%)
	5	✗	□	□	3 (2.7%)	3 (2.5%)	6 (2.6%)
	6	✗	✗	□	2 (1.8%)	0 (0%)	2 (0.9%)
	7	✗	□	✗	25 (22.1%)	27 (22.9%)	52 (22.5%)
	8	✗	✗	✗	47 (41.5%)	71 (60.2%)	118 (51.1%)

Notes: Tick marks (□) indicate having sufficient, knowledge, a positive attitude, and behaviour or a decision to take aspirin. ✗ marks indicate having insufficient knowledge, and negative attitude, and behaviour or a decision to not take aspirin. Participants must have sufficient knowledge about aspirin for CRC prevention to make an informed choice. Additionally, they need to have an attitude concordant with their behaviour, i.e., a positive attitude and a decision to take aspirin (1), or a negative attitude, and a decision not to take aspirin (2). All other combinations of knowledge, attitude and behaviour are considered uninformed choices (3 to 8).

Table 4. Participant self-reported changed behaviours at 1-month and 6-months by study arm in the SITA trial

	Intervention	Control	Estimated effect size[1]		
Total participants	**129**	**132**			
Behaviours to reduce colorectal cancer risk	**% (n/N)**	**% (n/N)**	**Difference (95% CI)**	**Odds Ratio (95% CI)**	**p-value**
Talked my GP about taking aspirin					
1 month	30.4% (35/115)	12.0% (15/125)	18.4% (8.23 to 28.41)	3.45 (1.69 to 7.05)	<0.001
6 months	30.5% (36/118)	15.1% (18/119)	15.4% (5.21 to 26.14)	2.52 (1.31 to 4.85)	0.005
Changed my diet					
1 month	28.7% (33/115)	24.8% (31/125)	3.9% (-7.74 to 14.52)	1.19 (0.66 to 2.14)	0.563
6 months	33.9% (40/118)	35.0% (42/120)	-1.1% (-13.56 to 10.30)	0.94 (0.54 to 1.63)	0.814
Talked to my GP about quitting smoking					
1 month	18.5% (10/54)	14.0% (8/57)	4.5% (-7.20 to 19.94)	1.34 (0.42 to 4.31)	0.619
6 months	11.3% (6/53)	17.0% (9/53)	-5.7% (-17.26 to 08.34)	0.50 (0.14 to 1.82)	0.292
Quit smoking[2]					
1 month	30.9% (17/55)	27.6% (16/58)	3.3% (-1.30 to 20.27)	1.11 (0.47 to 2.62)	0.802
6 months	42.6% (23/54)	52.8% (28/53)	-10.2% (-31.19 to 5.93)	0.67 (0.30 to 1.50)	0.331
Spoke to GP about screening for colorectal cancer by FOBT					
1 month	29.6% (34/115)	17.1% (21/123)	12.5% (2.73 to 23.57)	2.17 (1.16 to 4.04)	0.015
6 months	22.9% (27/118)	26.7% (32/120)	-3.8% (-14.18 to 7.78)	0.83 (0.45 to 1.51)	0.537
Completed FOBT test					
1 month	13.9% (16/115)	14.4% (18/125)	-0.5% (-0.93 to 0.83)	0.95 (0.45 to 1.99)	0.895
6 months	23.7% (28/118)	28.6% (34/119)	-4.9% (-15.78 to 6.34)	0.77 (0.42 to 1.39)	0.380
Spoke to GP about screening for colorectal cancer by colonoscopy					
1 month	14.8% (17/115)	14.5% (18/124)	0.3% (-10.33 to 9.37)	0.97 (0.46 to 2.01)	0.925
6 months	20.4% (24/117)	20.8% (25/120)	-0.4% (-10.48 to 10.05)	1.03 (0.53 to 1.98)	0.940
Had a colonoscopy					
1 month	11.2% (13/116)	6.5% (8/124)	4.7% (-2.44 to 11.63)	1.79 (0.70 to 4.55)	0.225
6 months	13.6% (16/118)	11.7% (14/120)	1.9 (-6.31 to 10.32)	1.22 (0.57 to 2.63)	0.611

n=the number participants who self-reported 'yes' to each of the behaviours; N=the total number of participants who provided a response to this item in the follow-up questionnaires.

[1] Estimated using logistic regression for each outcome, adjusted for general practice, sex and mode of delivery using only participants who completed follow-up

[2] This question was only asked to people who either had a history of smoking cigarettes or smoked cigarettes at baseline. There were 63 participants in the intervention arm and 61 in the control arm.

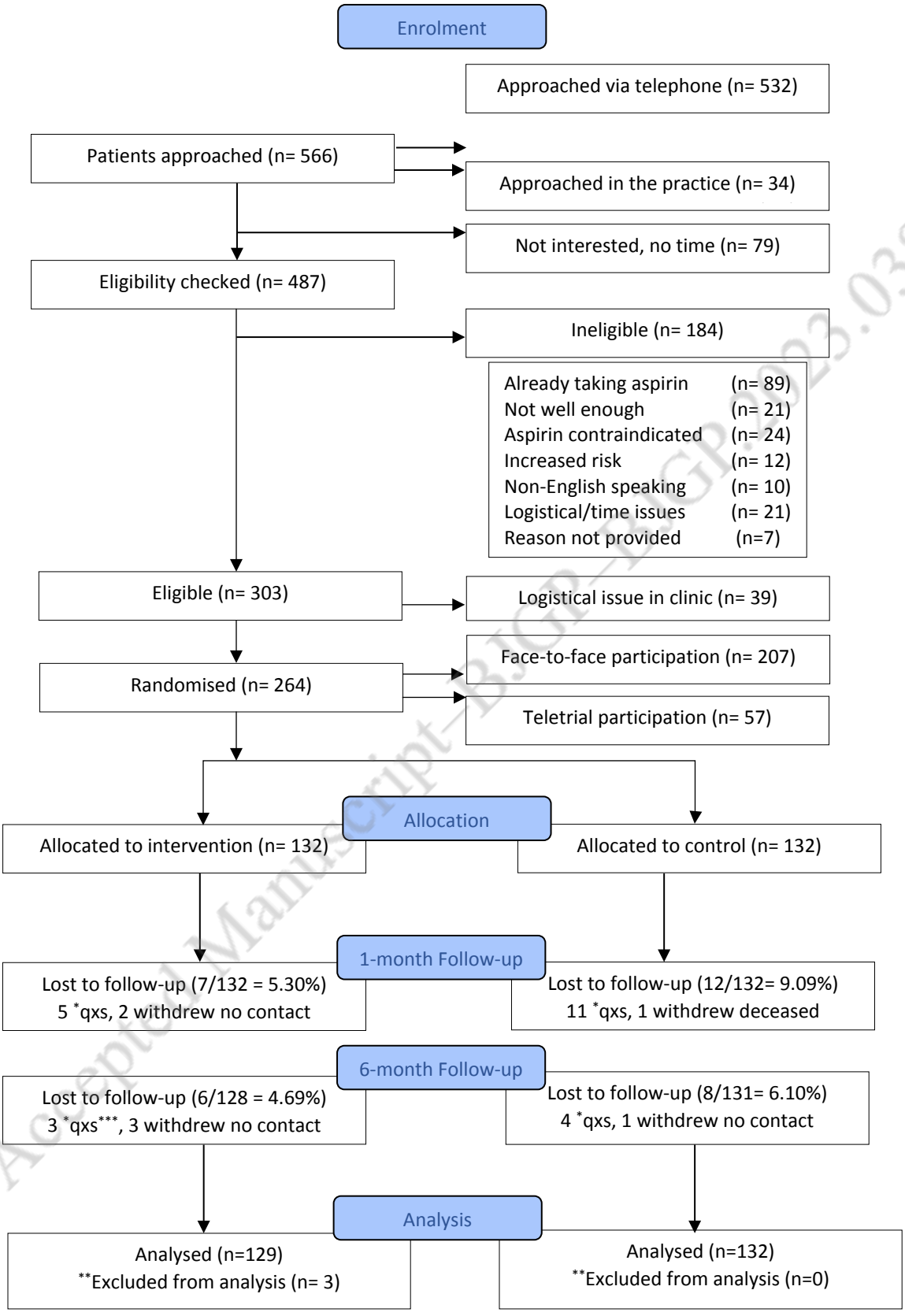

Figure 1. Participant flow diagram. *Number of follow-up questionnaires not completed. **Participants excluded after randomisation as researchers became aware of them taking blood thinners which were contra-indicated for aspirin, they were excluded from the trial. Number of participants included in the analysis. ***Follow-up questionnaires.