Appendix 1: Protocol

Technology Assessment Report commissioned by the NETSCC HTA Programme

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1. Title: The psychological consequences of false positive mammograms

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3. Plain English Summary

In the UK women aged 50 to 70 years old are invited to come for mammography screening every three years. About 5% of these are recalled for further investigation. After follow-up it is found that about 82% of recalled women had nothing wrong with them (false-positives). However, the experience of being unnecessarily recalled can be distressing, not just in the short-term but may lead to enduring anxiety and affect attendance at future routine mammography screening. The purpose of this systematic review is to find out what the research evidence is for medium and long-term effects of having a false-positive mammogram on mental health and behaviour, whether some groups of women are more likely to be adversely affected than others and if there are ways of reducing the negative effects of being recalled when you are in fact well.

4. Decision problem

The purpose of this technology assessment is to conduct a systematic review, to identify the psychological and behavioural consequences following false-positive screening mammogram results that affect women and any evidence for the effectiveness of interventions designed to reduce these. In particular we will be looking at whether the psychological and behavioural consequences or the effectiveness of specific interventions differ in different groups of women.

This research is necessary because of the large number of false-positive results that come from routine mammography screening. In the UK women aged 50-70 years, on population registers, are invited for mammography every three years through the NHS Breast Screening Programme (NHSBSP). Around two million women were screened by the NHSBSP in 2007/8 and of these 95,006 (5%) were recalled for further investigation; 16,735 cancers were detected leaving 78,271(82%) false-positive recalls.[1]

Quantitative observational studies looking at the psychological and behavioural consequences of false-positive mammograms show conflicting results. Some studies indicate that, whilst women show increased distress between receiving the information about the need for a follow-up appointment and receiving the all-clear, in the longer term their anxieties about breast cancer and mammography are not increased.[2-4] Other studies report that there are long-term adverse psychological consequences to receiving a false-positive mammogram.[5-8] The outcomes of studies looking at whether having false-positive results affects future attendance at breast screening appointments is similarly conflicted.[7;9-11]

A quantitative systematic review in 2007 by Brewer and colleagues found that the impact of a false-positive mammogram on subsequent screening attendance varied with nationality; although the reasons for this were unclear. They also reported a varying impact on long-term psychological distress, anxiety and depression, and other behaviours such as frequency of breast self-examination.[12] However, their review did not report the reasons for this variation in response. Furthermore, Brewer and colleague's review found no statistically sound studies that investigated whether anxiety over a false-positive mammogram directly affects whether women return for routine screening or increase breast self-examination. There was little evidence about the effects on quality of life or trust of healthcare services and no evidence about whether women who felt anxious after a false-positive screening result replaced

routine screening attendance with breast self-examination.[12] We also do not know what meanings women attribute to a false-positive mammogram or how these may determine their behaviour when invited for further routine mammogram screening as qualitative evidence is lacking.

Therefore, there is uncertainty about the psychological impact of false-positive mammograms on women. We do not know what the mediators are of negative psychological and behavioural outcomes which may affect attendance at future mammography screening. There is a need to answer these questions to identify and evaluate studies of interventions to treat the effect of false-positive results, and identify whether these effects differ in women from different backgrounds. The answers will have important policy implications for the NHS in the provision of breast cancer screening services.

The questions that this systematic review will answer are:

1. What evidence is there for medium or long-term adverse psychological consequences of false-positive screening mammograms?

    1.1. Do the types of psychological consequences differ between different groups of women?

2. Are there interventions that reduce adverse psychological consequences?

For question one the population will be women who have received a false-positive result from routine mammogram screening in the UK and invited for further assessment. Where studies include a comparator this will be women who had a routine screening mammogram but who had a normal mammogram and were not invited for further assessment. A range of outcomes, including qualitative, will be considered that report psychological and behavioural measures over the medium and long-term. Where data permit, sub-group analyses will be conducted of different groups of women (including socio-economic status and ethnic group).

For question two the population and the outcomes will be the same as question one. The interventions will be those delivered to individuals to address the adverse psychological consequences of a false-positive mammogram result, including attendance at future routine breast screening. Where there are comparators this will be an absence of an individualized intervention in the same population. Where data

permit, sub-group analyses will be conducted of different groups of women (including socio-economic status and ethnic group).

It is intended that this should be a wide systematic review considering a range of study types including uncontrolled studies and qualitative research but excluding individual case studies. Recommendations will be made for future primary research.

5. Methods for selection of evidence of clinical effectiveness

A systematic review will be conducted using the principles of the NHS Centre for Reviews and Dissemination[13] including those for non-randomized and qualitative studies.[14]

5.1. Inclusion criteria

Question	Criteria	Specification	Notes
1 and 2	Population	Women who have received a false-positive result from routine mammogram screening in the UK and have been invited for further assessment	Where data permit we will look at sub groups including socio-economic status and ethnic group
2	Intervention	Those interventions delivered to individuals to address the adverse psychological and behavioural consequences of a false-positive mammogram result.	These are individual interventions not group ones
2	Comparator	An absence of an individual intervention in the same population	
1 and 2	Outcomes	Psychological and behavioural outcomes and those from qualitative studies	Including subsequent attendance at routine mammography screening and quality of life
1 and 2	Setting	UK	Secondary care
1 and 2	Study design	Systematic reviews, randomized, non-randomized, observational and qualitative studies	We will not consider individual case studies
1 and 2	Length of follow-up	At least one month from the 'all clear'	Measured over the medium to long-term. i.e. not the immediate response to receiving a false-positive result
1 and 2	Language	English language only	Non English language papers will be included in the searches and screened, so that the number of potentially includable foreign language papes is known.

5.2. Exclusion criteria

The following types of studies will be excluded: narrative reviews, editorials, opinion pieces, non English language papers, individual case studies, and studies only reported as posters or by abstract where there is insufficient information to assess the quality of the study.

5.3. Search strategy

Refer to Appendix 1 for the draft search strategy for MEDLINE.

The search strategy will comprise the following main elements:

- Searching of electronic bibliographic databases
- Internet searches
- Scrutiny of references of included studies
- Contacting experts in the field

Databases will include:

MEDLINE, EMBASE, Cochrane Library, Psychlit, Cinahl Ebsco, Web of Science, Science Citation Index Expanded, Conference Proceedings Citation Index, Sociological Abstracts, Applied Social Sciences Index, Sociological Abstracts, Applied Social Sciences Index and International Bibliography of the Social Sciences.

5.4. Study selection

Based on the above inclusion/exclusion criteria, papers will be selected for review from the titles and abstracts generated by the search strategy. This will be done independently by two reviewers; discrepancies will be resolved by discussion, with the involvement of a third reviewer if necessary. Although non English language papers will not be included in the systematic review due to resource limitations, they will be identified and any that meet the other inclusion criteria will be recorded with their language noted as the reason for their exclusion. Retrieved papers will again be reviewed and selected against the inclusion criteria by the same independent process.

5.5. Data extraction

Data will be extracted from included studies by one reviewer using a standardised data extraction form and checked by another reviewer. Authors of studies will be contacted to provide missing information, as necessary.

5.6. Quality assessment

Quantitative studies will be assessed for internal and external validity according to criteria suggested by the updated NHS CRD Report No.4, according to study type.[13;15]

Qualitative studies will have their quality assessed using a standard assessment tool, e.g. Mays and Pope 1995[16] and Popay and colleagues 1998[17], a number of these will be piloted to assess their suitability for the task.

6. Methods for analysis and synthesis of evidence of clinical effectiveness

6.1. Quantitative analysis and synthesis

Studies were assessed for internal and external validity according to criteria suggested by the updated NHS CRD Report No.4, according to study type.[13;15] The quality of systematic reviews was evaluated using the PRISMA statement,[18]. Individual RCTs were appraised with the CONSORT statement[19] and individual observational studies with STROBE guidelines.[20]

6.2. Qualitative analysis and synthesis

These studies will be analysed using meta-ethnography[21-23] supported by Atlas.ti6 software. Here the included studies' results are translated into one another, whilst preserving their original meaning, with an inductive and interpretive approach to allow comparison between them. Authors' interpretation of the primary study findings become the data, which are translated across studies by the reviewers to produce a synthesis of meaning allowing the production of higher order concepts.

6.3. Combined synthesis of quantitative and qualitative evidence

The results of the quantitative and qualitative analyses will undergo narrative synthesis to construct an explanatory framework.[24;25] In this method both types of data analysis undergo a further narrative synthesis of their combined data through a process of developing an explanatory theory, undertaking a preliminary synthesis, looking at the relationships between and within studies and evaluating the robustness of the synthesis.

7. Expertise in this TAR team

7.1. People

Name	Institution	Expertise
Mrs Mary Bond	PenTAG, University of Exeter	Systematic reviewing, psychology and project management
Dr Toby Pavey	PenTAG, University of Exeter	Systematic reviewing
Mrs Karen Welch	Karen Welch Information Consultancy	Information Specialist
Mr Chris Cooper	PenTAG, University of Exeter	Information Specialist
Dr Ruth Garside	PenTAG, University of Exeter	Qualitative evidence synthesis
Prof. Chris Hyde	PenTAG, University of Exeter	Diagnostics and public health

In addition to the research team, we will be receiving expert clinical advice from Dr Russell Davies Consultant Breast Radiologist (Royal Devon and Exeter Foundation Trust), Gillian Gray (Breast Care nurse Royal Devon and Exeter Foundation Trust), Dr Jim Steel Consultant Breast Radiologist and Prof Carl Roobottom, Consultant Radiologist (both at Derriford Hospital, Plymouth), Jenny Hewison a Professor of the Psychology of Healthcare, from the University of Leeds. We have two patient representatives, Kate Blackmore and Sue Milward who have both had experience of having a false-positive mammogram to advise us on the patient perspective.

7.2. TAR centre – PenTAG

This project is being conducted by The Peninsula Technology Assessment Group (PenTAG), which is part of the Institute of Health Service Research at the Peninsula Medical School, University of Exeter. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme and other local and national decision-makers including NICE. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, psychology, statistics and health economics. The Institute of Health Service Research is made up of discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme.

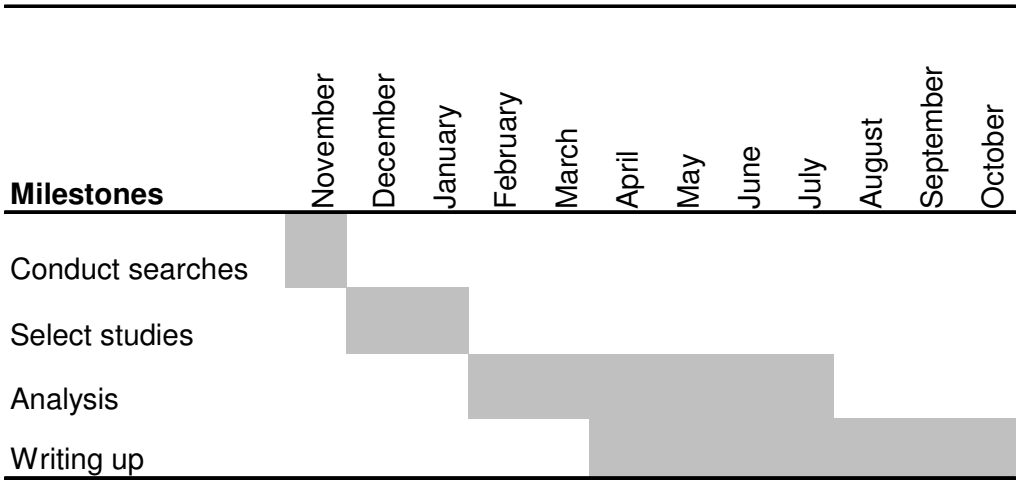
7.3. Contributions of team members

Name	Job title	Contribution
Mary Bond	Research Fellow in Health Technology Assessment	Providing project management. Writing the protocol. Conducting the systematic review. Writing and editing the report.
Toby Pavey	Research Fellow in Health Technology Assessment	Second reviewing the titles, abstracts and papers for the systematic review.
Karen Welch	Information Specialist	Writing and running the search strategies for the systematic review
Chris Cooper	Information Specialist	Writing and running the search strategies for the systematic review
Ruth Garside	Senior Research Fellow	Overseeing qualitative evidence synthesis
Chris Hyde	Professor of Public Health and Clinical Epidemiology	Director of the project and guarantor of the report. Contributing to editing the report.

8. Competing interests of authors

None.

9. Timetable and project milestones



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Appendix 2: Search Strategy

This is the original Medline search strategy by KW. Other search strategies are available from the authors on request.

Databases, Host Date Searched, Years	Search Strategy Keywords added to Refman	Number of Results
Medline Ovid Scoping Search 1950- current Searched on 08/10/2010	1. exp mammography/ae, px 2. exp mammography/ 3. FFDM.tw. 4. (mammogram* or mammograph*).tw. 5. (breast adj2 screen*).tw. 6. (breast adj2 scan*).tw. 7. "National Health Service Breast Screening Programme".tw. 8. NHSBSP.tw. 9. UK breast screen* program*.tw. 10. NHS breast screen* program*.tw. 11. Mass Screening/ 12. exp Breast Neoplasms/ 13. 11 and 12 14. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 13 15. False Positive Reactions/ 16. (false* adj3 positive*).tw. 17. "false-positive".tw. 18. "false-positives".tw. 19. (false adj3 test*).tw. 20. (false adj3 retest*).tw. 21. (retest* adj3 negative).tw. 22. diagnostic uncertaint*.tw. 23. or/15-22 24. exp Stress, Psychological/ 25. exp anxiety/ 26. exp fear/ 27. exp Depression/ 28. exp Emotions/ 29. Psychophysiologic Disorders/ 30. exp Psychology/ 31. exp Health Behavior/	559

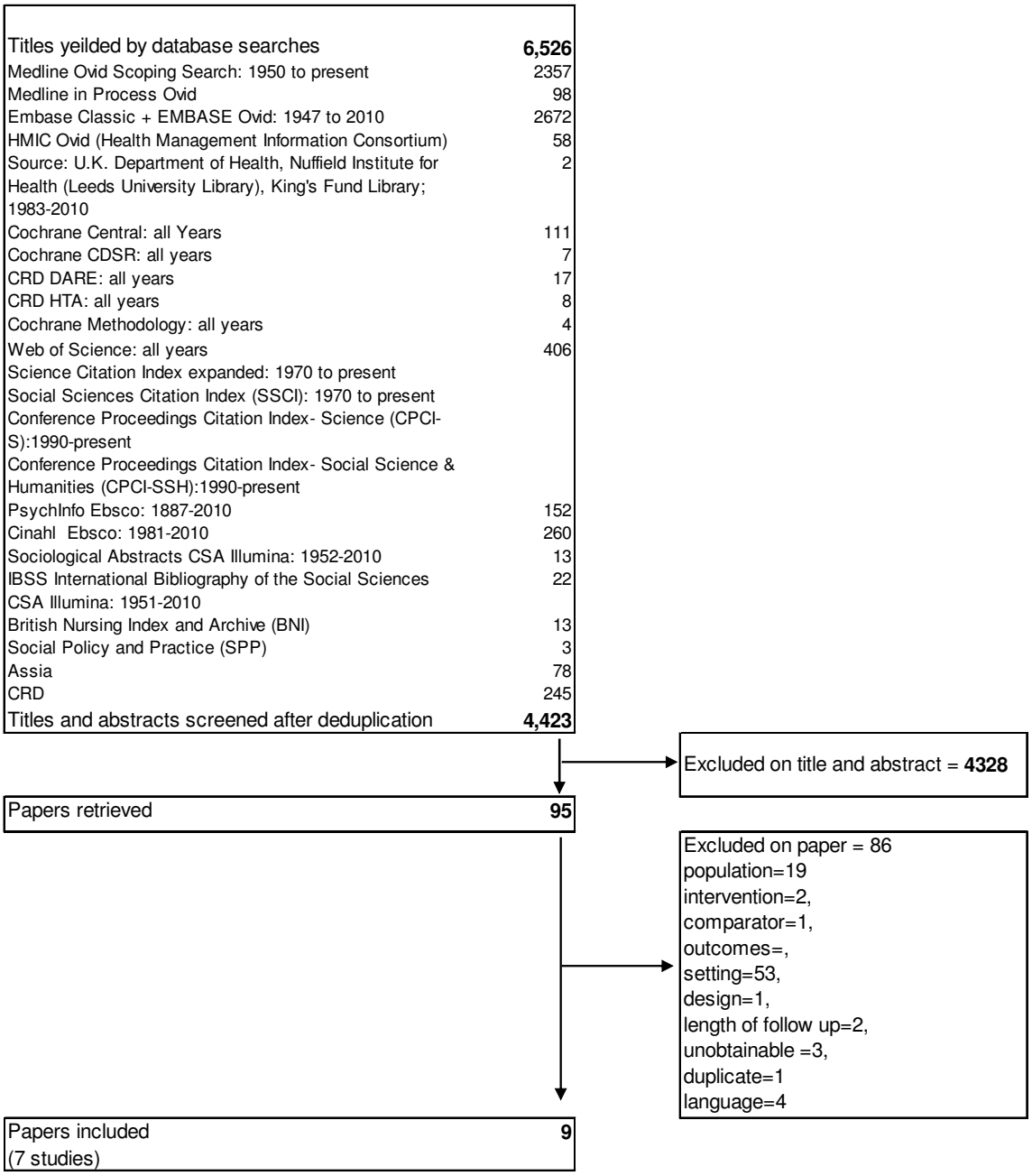
	32. exp Behavior/ 33. exp attitude/ 34. Motivation/ 35. Decision Making/ 36. exp "Quality of Life"/ 37. Health Knowledge, Attitudes, Practice/ or Attitude to Health/ or Patient Satisfaction/ or Patient Participation/ or Consumer Participation/ or Consumer Satisfaction/ or Sick Role/ or "Patient Acceptance of Health Care"/ 38. exp Affect/ 39. exp Affective Symptoms/ 40. (accept* or adhere* or affect* or anger* or anxiety or anxious or alarm* or attitude* or appetite or behavior* or behaviour* or belief* or believe* or comply or complian* or concordance or coping or concern* or confusion or confused or consequence* or consequential or conflict or cultural*).tw. 41. (demotivated or demotivation* or de-motivated or de-motivation* or disconcert* or depression or depressed or distress* or deleterious or disappointment or emotion* or ethnic* or ethnol* or experienc* or fear* or fright* or harm* or mental* or mistrust* or mood* or motivated or motivation* or nightmare* or perception* or perceive* or psychological or psychologically or psychology or psychosocial or reattend* or social*).tw. 42. "quality of life".tw. 43. (relief or relieved or risk*).tw. 44. (sleep or stress* or terror or terrified or trust* or mistrust*).tw. 45. (worry or worried).tw. 46. (wellbeing or "well-being" or "well being").tw. 47. or/24-46 48. exp Intervention Studies/ 49. exp Questionnaires/ 50. psychological tests/ or psychometrics/ or models psychological/ 51. Patient Education as Topic/ 52. health education/ or health promotion/ or health knowledge/	

	53. decision aid/ or decision support techniques/ 54. Educational Technology/ 55. audiovisual aids/ 56. telehealth/ or telemedicine/ or telecommunication/ 57. social support/ or self help groups/ or support groups/ 58. exp communication/ 59. persuasive communication/ 60. exp counseling/ 61. interviews as topic/ 62. evaluation studies as topic/ 63. qualitative research/ or program evaluation/ or process evaluation/ 64. focus groups/ 65. nursing methodology research/ 66. intervention*.tw. 67. (qualitative* or findings or evaluat* or synthes?s or meta-synthesis* or meta synthesis* or metasynthesis or meta-ethnograph* or metaethnograph* or meta ethnograph* or meta-study or metastudy or meta study or systematic* or "technology assessment" or sampl* or study or studies or observation* or research or discourse* or analys?s or humanistic or biographical or biography or narrative*).tw. 68. (support* or literature or booklet* or leaflet* or pamphlet* or letter* or video* or podcast* or telephon* or transtelephon*).tw. 69. (questionnaire* or interview* or discuss* or feedback or personalised or personalized or assessment* or reassurance or reassur*).tw. 70. (counsel* or education* or "informed choice" or "informed choices").tw. 71. "in person".tw. 72. (peer* adj5 (support* or group*)).tw. 73. ("expert patients" or "expert patients").tw. 74. (social adj network*).tw. 75. "emotional support".tw. 76. "family support".tw. 77. focus group*.tw. 78. ("one to one" or "one on one").tw.	

	79. ((patient* or consumer* or recipient* or client* or individual*) adj5 (communicat* or counsel* or inform* or education* or choice or discuss* or decision* or decide* or participat* or preference* or navigat*)).tw. 80. ((patient* or consumer*or recipient* or client* or individual*) adj5 (tailor* or personal*)).tw. 81. ((personal or interpersonal* or individual*) adj5 (decision* or choice* or preference* or participat* or preference*)).tw. 82. ((tailor* or individual* or personal*) adj5 message*).tw. 83. ((allocat* or allot* or assign* or divid*) adj5 (condition* or experiment* or intervention* or treatment* or therap* or control* or group*)).tw. 84. or/48-83 85. 1 and 23 and 84 86. 14 and 23 and 47 and 84 87. 85 or 86 88. 1 and 23 89. 14 and 23 and 47 90. 88 or 89 91. limit 90 to ("qualitative studies (sensitivity)" or "qualitative studies (specificity)" or "qualitative studies (optimized)") 92. limit 90 to systematic reviews 93. limit 90 to (case reports or clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or government publications or guideline or meta analysis or multicenter study or patient education handout or practice guideline or randomized controlled trial or "review" or "scientific integrity review" or technical report or twin study or validation studies) 94. 87 or 91 or 92 or 93 95. 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 64 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 96. 48 or 49 or 61 or 62 or 63 or 65 or 66 or 67 97. 14 and 23 and 47 and 95 and 96 98. 1 and 23 and 96	

	99. 14 and 23 and 47 and 96 100. 94 or 97 or 98 or 99 101. 94 or 100	

Appendix 3: Study flow chart



Appendix 4:Critical appraisal of included studies

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	1	2	3	4	5	6	7	8
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✗	✗	✗	✗	✗	✗	✗	✗
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	✓	✓	✓	✓	✓	✓	✓	✓
Introduction										
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	✓	✓	✓	✓	✓	✓	✓	✓
Objectives	3	State specific objectives, including any prespecified hypotheses	✓	✓	✓	✓	✓	✓	✓	✓
Methods										
Study design	4	Present key elements of study design early in the paper	✓	✓	✓	✓	✓	✓	✓	✓
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓	✓	✓	P	✓	✓	P	✓
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	✓	✓	✓	✓	✓	✓	✓	✓
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	NA	NA	NA	NA	NA	NA	NA	NA
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	NA	NA	NA	NA	NA	NA	NA	NA
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	NA	NA	NA	NA	NA	NA	NA	NA
		Case-control study—For matched studies, give matching criteria and the number of controls per case	NA	NA	NA	NA	NA	NA	NA	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓	✓	✓	P	P	✓	✓	✓
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓	✓	✓	✓	✓	✓	✓	✓
Bias	9	Describe any efforts to address potential sources of bias	✓	✗	✓	✗	✗	✗	✗	✗
Study size	10	Explain how the study size was arrived at	✓	✓	✓	✓	✗	NA	NA	✗
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✓	✓	✓	✓	✓	✗	✗	✓
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	✓	✓	✓	✓	✓	✗	✗	✓
		(*b*) Describe any methods used to examine subgroups and interactions	NA	NA	✓	NA	NA	✗	NA	NA
		(*c*) Explain how missing data were addressed	✗	✗	✓	✗	✗	NA	NA	✗
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	✗	✗	NA	✗	✗	NA	NA	NA
		Case-control study—If applicable, explain how matching of cases and controls was addressed	NA	NA	NA	NA	NA	NA	NA	NA
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	NA	NA	NA	NA	NA	NA	NA	✗
		(*e*) Describe any sensitivity analyses	NA	NA	NA	NA	NA	NA	NA	NA

1: Brett & Austoker (2001), 2:Brett et al. (1998), 3:Ong et al. (1997)a, 4:Bull & Campbell (1991), 5: Ellman et al. (1989), 6:McCann et al. (2002), 7:O'Sullivan (2001), 8:Orton et al. (1991). ✓: item present, ✗:item absent, P: item partially present, F: results only present as figures, NA: not applicable

Results			**1**	**2**	**3**	**5**	**6**	**9**	**10**	**11**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓	✓	✓	P	✓	✓	✓	✓
		(b) Give reasons for non-participation at each stage	✓	✗	NA	✗	✗	NA	NA	✗
		(c) Consider use of a flow diagram	✗	✗	NA	✗	✗	✗	✗	✗
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✓	✗	P	P	P	P	✗	✗
		(b) Indicate number of participants with missing data for each variable of interest	✗	✗	✓	✗	✗	NA	NA	✗
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	✓	✓	NA	✗	✗	NA	NA	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	✓	✓	NA	✓	✓	✓	✓	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA	NA	NA	NA	NA	NA	NA	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA	NA	✓	NA	NA	NA	NA	✓
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓	✓	✓	✓	✓	✓	✓	P
		(*b*) Report category boundaries when continuous variables were categorized	NA	NA	NA	✓	✓	NA	NA	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	✗	✗	NA	NA	NA	NA	NA	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA	✓	✓	NA	NA	NA	NA	NA
Discussion										
Key results	18	Summarise key results with reference to study objectives	✓	✓	✓	✓	✓	✓	✓	✓
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✗	✓	✗	✗	✗	✗	✗	✗
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓	✓	P	✓	P	✓	✓	✓
Generalisability	21	Discuss the generalisability (external validity) of the study results	✗	✗	✗	✗	✗	✗	✗	✓
Other information										
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓	✓	✓	✗	✓	✓	✓	✗

1: Brett & Austoker (2001), 2:Brett et al. (1998), 3:Ong et al. (1997)a, 4:Bull & Campbell (1991), 5: Ellman et al. (1989),6:McCann et al. (2002), 7:O'Sullivan (2001), 8:Orton et al. (1991). ✓: item present, ✗:item absent, P: item partially present, F: results only present as figures, NA: not applicable

✓	**item present**
✗	**item absent**
P	**item partially present**
F	**results only presented as Figures**
NA	**not applicable**

Meldrum et al. 1994. CONSORT statement			
Section/Topic	**Item No**	**Compliant**	**Checklist item**
Title and abstract			
	1a	Yes	Identification as a randomised trial in the title
	1b	Yes	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)
Introduction			
Background and objectives	2a	Yes	Scientific background and explanation of rationale
	2b	Yes	Specific objectives or hypotheses
Methods			
Trial design	3a	Not reported	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	NA	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Yes	Eligibility criteria for participants
	4b	Yes	Settings and locations where the data were collected
Interventions	5	No	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Yes	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	NA	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	Yes	How sample size was determined
	7b	NA	When applicable, explanation of any interim analyses and stopping guidelines
Randomisation:			
Sequence generation	8a	Yes	Method used to generate the random allocation sequence
	8b	Not reported	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Not reported	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Not reported	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	11a	Not reported	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
	11b	Yes	If relevant, description of the similarity of interventions
Statistical methods	12a	Yes	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Yes	Methods for additional analyses, such as subgroup analyses and adjusted analyses
Results			
Participant flow (a diagram is strongly recommended)	13a	Yes	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	No	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Yes	Dates defining the periods of recruitment and follow-up
	14b	NA	Why the trial ended or was stopped
Baseline data	15	F	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	Yes	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	Yes	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	NA	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	NA	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	Not reported	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)
Discussion			
Limitations	20	Not reported	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalisability	21	Not reported	Generalisability (external validity, applicability) of the trial findings
Interpretation	22	No	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other information			
Registration	23	Pre-registry	Registration number and name of trial registry
Protocol	24	No	Where the full trial protocol can be accessed, if available
Funding	25	Yes	Sources of funding and other support (such as supply of drugs), role of funders