Author’s response to reviews

Title: Screening to Prevent Fragility Fractures Among Adults 40 Years and Older in Primary Care: Protocol for a Systematic Review

Authors:
Jessica Morgan (jess.morgan@york.ac.uk)
Melissa Harden (melissa.harden@york.ac.uk)
Robert Phillips (bob.phillips@york.ac.uk)

Version: 1 Date: 30 May 2019

Author’s response to reviews:

Dear Sirs/Mesdames,

Thank you very much for your thoughtful and constructive feedback to our ‘Does routine surveillance imaging after completing treatment for childhood solid tumours cause more harm than good? A Systematic Review & Meta-Analysis Protocol.’ We have carefully considered each of your comments and provide our responses below, in the order of your reports.

Reviewer #1:

This protocol is for a much needed systematic review. The authors should be commended by having involved patients in the design of the protocol ensuring that the outcomes are relevant to the patients.

The recommendation for major review is based on a number of issues that are mostly unclear. I provide below a set of comments to each section of the protocol, which broadly cover three topics:

1) Is unclear whether the review will include children, adolescents and young adults, or just children. Please provide a clear and consistent definition throughout the manuscript.

We apologise for the lack of clarity here. The review includes children, adolescents and young adults, under the age of 25 years. We have attempted to clarify this by adding the following sentence on page 5: “For the purpose of this review, the term “child” or “childhood” refers to any child, adolescent or young adult up to the age of 25 years.”
2) It is unclear if studies without a comparison group are to be included, as some of the information in the methods and analysis sections are contradictory (see comments below).

Again, we apologise for any confusion. Any study with, or without, a comparison group is eligible for inclusion.

3) The objectives and outcomes refer to cost-effectiveness measures, but none of these data are addresses in the data extraction and synthesis. This is essential information to be set out in the protocol. Please note that the review is already ambitious without including this objective, and the authors could consider a separate review on the topic.

We have clarified this within the synthesis section. Cost-effectiveness data would already fit within the current data extraction form within the section “secondary outcome(s), including definition of each” and, as we have not mentioned any other outcomes specifically here, we have not done so for cost-effectiveness. We do not anticipate significant, high quality, cost-effectiveness data and therefore do not feel that this adds substantially more work to this review.

Introduction

The introduction provided a reasonable justification for why this work is needed, but it would help if they could clarify if there are specific guidelines for which imaging studies are to be done, and how often. I presume that these don’t exist, which could be stated as an additional point to justify their work.

There are no specific guidelines for imaging, outwith clinical trial requirements. We have added a phrase to the end of the first sentence “and directed by local protocols and traditions” which communicates this issue. We have added a sentence to this effect.

In this section and in the title, the author refer to childhood cancers; this is inconsistent with the methods, where the authors refer to plans to include studies with patients up to 25 years of age. The patient population under study should be clearly described from the beginning. If adolescents and young adults are to be included, do they have the same experience as children?
As previously expressed, we have added a sentence to clarify the use of the words “child” or “children”. The malignancies experienced by children and young adults are often similar biologically, and in many places the teenage/young adult population are treated in the same services as children, thus their experiences are often similar. This inclusion of teenage/young adult populations within paediatric groups is common in the paediatric oncology world and, though the exact cut-off can (and has) been debated, this is an accepted point for delineation within the clinical area.

On the penultimate paragraph of the introduction, the authors talk about the monetary costs of the investigations. The costs for the patients/relatives go beyond the transport and parking, including loss of work productivity, and are will vary likely to vary by type of health service (public or private). The authors mention restricting to review to studies reporting on patients in high-income countries; I wondered if countries where private health care is available (e.g. the US) will have different practices on this.

Thank you. We have added an additional phrase to the family costs. We do not anticipate many data surrounding the health economics of this area. If there was the data to explore this according to type of health service, we would happily evaluate this within the sub group analyses and have added a sentence to this effect.

The paragraph in lines 9-13 should be replaced by the aims paragraph in p. 7. The points the authors made in this paragraph would be better suited for the discussion.

We appreciate the reviewer’s opinion as to the structure of this introduction. After further consideration, we believe the introduction, with other modifications, is better with this paragraph in situ to orientate the reader unfamiliar with the topic to read the rest of the review more clearly.

Patients and public involvement

The second, third and fourth paragraphs on p. 6 are better suited for the discussion. The first paragraph could be integrated in the methods section, in the sub-section for Outcomes.
The most appropriate situation of PPI reporting within manuscripts has not been clearly defined within the literature. As authors, we feel strongly that this section should remain at the start of the paper, given that the PPI work came before the construction of the methods and has strongly informed and influenced the methods chosen. This should be recognised up front and we do not feel is an outcome of the review, but instead an integral part of the protocol formulation, and informed our selection and definition of the review outcomes.

Methods

Could the authors clarify the rationale for searching both MEDLINE and Pubmed, as the former is included in the latter?

To ensure that our searches did not miss relevant studies we searched PubMed in addition to Ovid MEDLINE. PubMed contains extra records that are not included in Ovid MEDLINE as outlined here by the National Library of Medicine https://www.nlm.nih.gov/bsd/disted/pubmedtutorial/010_070.html. At the time that the searches were carried out in July 2018 we were aware of one particular relevant paper https://www.ncbi.nlm.nih.gov/pubmed/29960848 that was in PubMed but not in Ovid MEDLINE.

The authors are to be commended in their intentions to include abstracts from conferences, but are advised to consider the potential contribution of these works (as especially they are looking to include RCTs) that provide little detail in methods and results, and are unsuitable for a sound assessment of risk of bias. Risk of bias is unlikely to be introduced in this review by leaving these short publications out.

We appreciate the discussion regarding risks and benefits of including conference abstracts within the findings. As this is likely to be an under-researched area of practice, there is a risk of missing data without including conference abstracts. We would prefer to search for and identify conference abstracts, then explore their impact on the data through risk of bias assessment and sensitivity analysis, rather than excluding outright.

Appendix 1 outlines the criteria to judge the studies but is unclear how point 6 is to be applied. I presume the study will have to meet all criteria previously specified?
This indeed is correct. We have added a sentence to the appendix to clarify this.

Methods, Inclusion and exclusion criteria: the first paragraph should either be deleted or moved elsewhere.

We have deleted this as requested.

In the study design section, the authors refer to including the study design in an 'iterative way'. I think this should be discouraged for several reasons: how will the authors decide what are sufficient studies of these designs? In addition, for the main outcome of this review (overall survival), the studies will be prospective in nature, even if retrospective in design (e.g. a retrospective cohort study).

We do recognise this is a rather troublesome approach within the common approach to evidence synthesis. We have undertaken a number of reviews in this area, and have found that rather than undertaking a review with a fixed ‘bar’ of study design/quality, discovering insufficient data, and needing to undertake a further review, a more efficient approach it to use this iterative, hierarchical approach. The ‘sufficiency’ of the data is, in a similar way to other concepts of saturation in qualitative and adequate precision in quantitative assessments, a judgement based on the context of the information described and the confidence in the findings. The review team, including PPI input, will use an approach based on clinical reason to determine sufficiency.

We disagree that all these studies will be prospective. Of course, survival occurs going forwards in time, but a retrospective cohort may be formed by from records drawn from a variety of types of sources and may omit important information, including absence of unknown survival status, a ‘missing unknown’, unlike those where entry is determined by a prospective study design even if the analysis of the benefit of a surveillance programme is a secondary (‘retrospective’) data analysis.

In the population paragraph, could you please clarify the difference between 'ongoing disease' and 'residual abnormalities that are deemed to be stable'?
This is indeed a difficult area, and one which occasionally cause consternation for practicing clinicians. Ongoing disease refers to a state where there is reasonable certainty the malignant process is continuing, in a detectable manner. Residual abnormalities are seen in some conditions (for example, Hodgkin Lymphoma) without evidence of active disease (for example, by an absence of symptoms, no change in size over time, metabolic quiescence). As such, it is a decision only able to be made by the treating team at the time, and the challenges in the variation in this will be one of the sources of heterogeneity which could need to be addressed.

Please provide a specific cut-off for 'the majority of patients aged…'; you included one in the study assessment form, which should be clarified here.

Thank you, we have clarified this information (note: the cut off was changed following piloting of the study assessment form and hence is now >50%).

Finally, if studies from LMIC are not being included in this review, this should be clarified before, possibility in the objectives, as the authors refer to no restriction regarding geography in the search strategy.

Indeed, no geographical limitation was included within the search as these are not yet fully developed as a methodology with database searching and risk excluding studies that would be of interest. Application of geographical limits are therefore best performed within the screening phase of a review. We have included the phrase “in high-income countries” within the aims and objectives.

In the description of the intervention and comparators section, could the authors explain why they chose to include only studies where the result of the surveillance programme was the main outcome of the study? In addition, the first sentence of the last paragraph of this section is better suited for the patient population. The second sentence of the same paragraph could be deleted or incorporated in the first paragraph.

The inclusion of studies specifically reporting on the value of a surveillance programme is pragmatic, and based on our initial review of the literature in this field. While treatment trials do indeed mention relapse rates, event free and overall survival, they do not describe the follow-up
programmes or outcomes related to the mode of detection. To ensure the review is practical, we have chosen to include only those papers where the data may be found, using a similar risk/benefit model to using a search ‘filter’ which may be 99% sensitive for clinical trials, yet makes the numbers of papers screened manageable. With respect to the sentence, we have moved them as requested.

The list of outcomes does not specify 'mortality from recurrence', as specified in the objective. In addition, please note the difference between survival and mortality. Mortality refers to whether death is observed or not; survival implies a length of time between the date of diagnosis and the date of death. Age at time of death is a problematic measure of survival because it only indicates the upper extreme of the survival time interval.

Thank you for highlighting this. We have removed “mortality from recurrence” from the manuscript. We do not quite understand the ‘age at death’ as an upper extremity of the survival interval; we are attempting to express a measure of duration of life in children affected by cancer as an approach to a measurement avoiding any lead-time bias from early detection without any change in the trajectory of the relapsed disease.

In inclusion/exclusion criteria for qualitative studies, please integrate lines 13 to 16 into the previous section (participants).

We have adjusted this as requested.

The language criteria are substantially different from the ones for quantitative studies, and is unclear why. In particular is unclear if the authors want to include only papers written in English or whose subjects of the research spoke English. Please note that papers in English mat include accurate translations from patients whose spoke other languages, and that you said you would seek translation for quantitative studies.

Thank you, we have clarified that we will include only studies where data is collected in English. Whilst translation of qualitative data from one language into another may be correct in terms of “word for word” translation, the concepts captured are often firmly situated within culture and language traditions that may result in meaning being lost when moving to the English language. This is not the case for quantitative data and thus means that the two forms should be managed
differently. It should be noted that we do not expect large quantities of qualitative data within this review.

Please provide a section for data extraction and another for risk of bias assessment. In the data extraction, briefly provide the main variables that will be extracted from quantitative and qualitative studies, and what is meant by 'technique for derivation'.

We have split these sections as requested. Planned data variables for extraction are included in Appendix 2. We have clarified the bracketed term to now read “with the technique used for derivation of cut-points”, in recognition that the method used can result in different cut-points being selected.

In the section for the risk of bias assessment, I would discourage the use of modified version of the tools, as the validity of the ascertainment of studies which have 'low to moderate' risk of bias is unknown. The authors might consider identifying the main domains that may interfere with the quality of the studies in the review and define criteria to classify the studies as at low risk, high risk, or unclear risk of bias.

We do appreciate the tension between using the full ROBINS-I tool and an unvalidated version. Our preliminary scoping suggests the studies will almost exclusively have high risks of bias and have few comparative elements. The pragmatic solution is to use a tool shaped to this end. Should a surprisingly high quantity of good, comparative, studies emerge this will be revisited and a protocol amendment issued.

When authors are to be contacted, please specify which author is going to be contacted and how many attempts will be made for emails that fail to be delivered.

We have provided the information regarding the author to be contacted.

In the analysis section, please remove sentences the sentences in lines 20-23 (there is no need to state the objective again).
We have removed this as requested.

Provide a detailed analysis plan depending on the type of data possibly available for narrative analysis. In the meta-analysis section, please explain what type of data will be input into the meta-analysis and the analytic method of choice to calculate the summary effect estimate. Please justify the choice of random over fixed methods meta-analysis. The sentence in line 7-8 is unnecessary and, if included, should be moved upper in the manuscript.

The meta-analysis will be based on a ratio measures or survival duration, if provided, and only if sufficient clinical homogeneity exists. We seriously doubt this will be possible. Inverse variance random effects meta-analysis, using methods of first converting log-rank estimates into log hazard ratios, will be used given the anticipated clinical heterogeneity in terms of population and intervention. We have moved the mentioned sentence to the first paragraph of the analysis section. We have added further details to the narrative analysis plan.

Sentence on line 11 is incomprehensible; please note the differences in the definitions of observed survival and hazards ratio. Please provide a detailed of the 'weighted mean differences' that will be calculated, and what are the weights to be used. The assessment of heterogeneity section should be part of the meta-analysis section.

We apologise for adding such a weak line to the protocol. While we doubt the data will exist, we will undertake an inverse variance meta-analysis of median survival times. We have deleted the subheading “assessment of heterogeneity”.

Lines 19-22 repeat lines 9-10; perhaps delete the latter. For all characteristics under 'subgroup analysis' please keep only the relevant information for this section, and move the explanation of why you think that those results are important to the discussion.

Thank you. We have deleted lines 9-10 instead of lines 19-22 as we feel the flow is better within the analysis section in this way. We have chosen not to move the discussion of characteristics as we feel the justification for these choices is best left associated with where the choices are enacted. We have limited the discussion to the potential impacts of the systematic review.
The current text makes it difficult to understand what exactly is going to be analyzed and how. Please note that the analysis should clearly identify how each specific outcome is going to be analyzed.

We hope that the adjustments made according to these comments have clarified the analysis plan for the reviewer.

In the assessment of publication bias, please clarify what will be considered 'sufficient comparative studies'. The information throughout the manuscript is inconsistent on whether studies with no comparison group are included or excluded. Similarly, it is unclear whether studies whose main outcome is not one of the outcomes for this review (secondary analysis) are included or excluded.

Thank you – we hope we have now clarified this by changing ‘sufficient’ to “≥5 comparative studies reporting the same outcome”. Studies with no comparison group are eligible for inclusion. We trust this has been made clearer on page 10. Studies whose main outcome was not one of the review outcomes would not be eligible for inclusion (studies must meet all inclusion criteria to be eligible for inclusion.

Discussion

Please provide an opening sentence that is neutral as to whether the results will be positive or negative, because either way they will be relevant. It is okay to discuss the potential impact of the different conclusions.

Thank you. We have added a neutral opening sentence. We have re-arranged the following paragraphs accordingly.

Other minor points

* P. 4, paragraphs 2 and 3 should be joined.

    We have done this as requested.

* P. 4, lines 20-23: is the risk increased in children, adults, or both?
The risk is increased in both adults and children. However, as this review only addressed children, teenagers and young adults, we have only addressed the information relating to this group.

* P. 5, line 3: you mention that the imagining may add unnecessary distress to the family. I recommend adding 'and to the patients'.

We have added this clause.

* Please provide the full reference for reference 4.

Thank you. We have done this.

1. * Please number the appendices.

We have done this as requested.

* Appendix 1, point 5 - this could be clarified that you refer to the outcomes of the present review; the current wording is ambiguous in what study protocol is being considered.

We have clarified by adding the word “review” to the question.

* P. 9, lines 1-20: please provide a full sentence, explaining that those children are the ones eligible for the study.

We have clarified this by adding the words “Studies will be eligible for inclusion if they include”.

* P. 16 - line 19: please provide a reference for the test.

Thank you. We have done so.

* P. 23 - includes an option for hereditary syndromes, which the text say will be excluded (and thus no need to have their data extracted)
As we expect that many studies will include a heterogeneous group of patients (which may include those with hereditary predisposition syndrome) including those who would typically be excluded, this question allows the collection of data such as “2% of patients had hereditary predisposition syndromes but were not reported separately so could not be excluded from the results.” We have added the words “any patients with” to provide some clarification.

* P. 25 and 26 are not referred to in the text. These could be excluded, as it goes beyond what is needed for this protocol and likely different from the final ones.

    Thank you. We have deleted these pages.

Reviewer #2: I would like to congratulate you on this protocol, and to wish you the best of luck for its conclusion.

This article is well written, with enough detail regarding the systematic review process - inclusion criteria and their justification, items for extraction, respect of PRISMA guidelines and evaluation of bias and quality of articles, therefore allowing for the replication of the process. The planned statistical analysis is appropriate for the theme and for the potential data obtained from the articles. The implications and dissemination of the results is also clear and shows the importance of this theme to the stakeholders and societal groups.

I have only two aspects to point out. First is regarding the exclusion of articles from LMI countries; although I understand the reasons for this, I would like to see this a bit more discussed, namely, the potential problems that the inclusion of articles from these countries might create.

    Thank you for your kind comments. We hope that we have added additional clarity on page 10 to address this point.

The second is regarding the data extracted from the qualitative studies. Although the data extraction tool is quite detailed, I was wondering if any particular qualitative method will be used, as content or thematic analyses. If yes, this should be made explicit.

    Thank you for identifying this omission on our part. We have added a brief section on page 17 to address this point.
We hope that these comments provide a comprehensive response to your concerns. We would be happy to provide details on any further issues that you wish us to clarify.

Yours sincerely,

The Authors