APPENDIX A. SEARCH STRATEGIES

MEDLINE & EMBASE

Key Question 1&2

	Search Terms
1	Exp lung neoplasms/di, rt, su, th [diagnosis, radiotherapy, surgery, therapy]
2	Non-small-cell lung carcinomas.tw
3	Non-small cell lung cancer.tw
4	Nsclc.tw
5	OR/1-4
6	Radiation Dose Hypofractionation/ or (radiotherapy minibeam$1 or radiation hypofractionated dose or radiation dose hypofractionation or hypofractionated radiation therapy or short?course radiation therapy).ti,ab.
7	dose fractionation/ or dose response relationship, radiation/ or radiotherapy dosage/
8	((radiotherapy* or radiat*) adj2 (dose or dosage or regimen* or schedule*)).tw.
9	hypofractionat*.mp.
10	hypo-fraction*.mp.
11	multi-fraction*.tw.
12	(hypo adj3 fraction*).tw.
13	Stereotactic body radiation therapy/ or SBRT.mp.
14	Stereotactic ablative body radiation therapy/ or SABR.mp.
15	(Stereotactic body radiation therapy or SBRT).tw.
16	(Stereotactic ablative body radiation therapy or SABR).tw.
17	Exp radiosurgery/
18	Or/6-17
19	Lung cancer terms and SBRT (5 and 18)
20	(thoracic surg*).tw,kw.
21	Lobectomy.tw
22	Video-assisted thoracoscopic surgery.tw
23	VATS.tw
24	Posterolateral thoracotomy.tw
25	Sublobar resection.tw
26	Segmentectomy.tw
27	Sublobectom or wedge resection.tw
28	Segmental resection.tw
29	Limited resection.tw
30	Or/20-29
31	Lung cancer terms and Surgery (5 and 30)
32	Randomized controlled trial.pt. or randomized.mp. or placebo.mp.
33	Randomized controlled trial/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/

34	('clinical trial' or 'randomized controlled study' or 'randomized controlled trial' or 'double blind clinical study' or 'single blind clinical study' or 'random allocation').ti,ab.
35	Or/32-34
36	19 or 31
37	35 and 36
38	Limit 37 to English language
39	Limit 38 to yr=”2000-current”

Key Question 3

	Search Terms
1	Exp lung neoplasms/di, rt, su, th [diagnosis, radiotherapy, surgery, therapy]
2	Non-small-cell lung carcinomas.tw
3	Non-small cell lung cancer.tw
4	Nsclc.tw
5	OR/1-4
6	exp cryosurgery/
7	exp Radiofrequency Therapy/
8	(((radiofrequency or microwave) adj1 ablation) or brachytherapy).tw.
9	Exp brachytherapy/
10	(Microwaves exp Mesh Term/ OR microwaves.tw OR "Radio Waves" exp Mesh Term/ or Radiowaves.tw or "radio waves".tw) OR (("Radiowaves".tw OR "Radio Waves".tw) AND "ablation".tw)
11	(Cryoabalation.tw OR Cryoprobes.tw OR Cryotherapy Mesh Term/ OR Cryotherapy.tw OR Cryosurgery.tw OR Cryogen*.tw)
12	Or/6-11
13	Lung cancer with other treatment (5 and 12)
14	Limit 13 to English language
15	Limit 14 to yr = “2000-current”

AHRQ, COCHRANE, VA ESP KEYWORDS

Lung cancer, lung malignancy, malignant, lung, radiotherapy, ablative therapy

APPENDIX B. EXCLUDED STUDIES

KEY QUESTIONS 1 & 2

1. Aridgides P, Bogart J. Stereotactic Body Radiation Therapy for Stage I Non-Small Cell Lung Cancer. *Thoracic Surgery Clinics*. 2016;26(3):261-269. *Ineligible publication type*
2. Bahig H, Chen H, Louie AV. Surgery versus SABR for early stage non-small cell lung cancer: The moving target of equipoise. *Journal of Thoracic Disease*. 2017;9(4):953-956. *Ineligible publication type*
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5. Fernando HC, Timmerman R. American College of Surgeons Oncology Group Z4099/Radiation Therapy Oncology Group 1021: a randomized study of sublobar resection compared with stereotactic body radiotherapy for high-risk stage I non-small cell lung cancer. *The Journal of thoracic and cardiovascular surgery*. 2012;144(3):S35-8. *Ineligible publication type*
6. Franks KN, McParland L, Webster J, et al. SABRTooth: a randomised controlled feasibility study of stereotactic ablative radiotherapy (SABR) with surgery in patients with peripheral stage I nonsmall cell lung cancer considered to be at higher risk of complications from surgical resection. *The European respiratory journal*. 2020;56(5). *Ineligible outcome*
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10. Herrmann MKA, Bloch E, Overbeck T, et al. Mediastinal radiotherapy after multidrug chemotherapy and prophylactic cranial irradiation in patients with SCLC--treatment results after long-term follow-up and literature overview. *Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique*. 2011;15(2):81-8. *Ineligible intervention*
11. Love SM, Hardman G, Mashar R, Shah RD. Is it time for SABR to overtake surgery as the treatment of choice for stage I non-small cell lung cancer? *Annals of Translational Medicine*. 2016;4(24):535. *Ineligible publication type*
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13. Nieder C, Andratschke NH, Guckenberger M. A pooled analysis of stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small cell lung cancer: is failure to recruit patients into randomized trials also an answer to the research question? *Annals of translational medicine*. 2015;3(11):148. *Ineligible publication type*
14. Onaitis MW, Salama J. Surgery versus stereotactic body radiation therapy for operable stage i non-small cell lung cancer: Can we achieve equipoise? *Journal of Thoracic and Cardiovascular Surgery*. 2016;152(1):1-2. *Ineligible publication type*
15. Parashar B, Port J, Arora S, et al. Analysis of stereotactic radiation vs. wedge resection vs. wedge resection plus Cesium-131 brachytherapy in early stage lung cancer. *Brachytherapy*. 2015;14(5):648-54. *Ineligible study design*
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KEY QUESTION 3

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APPENDIX C. RISK OF BIAS RATINGS (KQ1 ONLY)

Publication	Trial	Domain 1: Risk of Bias Arising from the Randomization Process	Domain 2a: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Assignment to Intervention)	Domain 2b: Risk of Bias Due to Deviations from the Intended Interventions (Effect of Adherence to Intervention)	Domain 3: Risk of Bias Due to Missing Outcome Data	Domain 4: Risk of Bias in Measurement of the Outcome	Domain 5: Risk of Bias in Selection of the Reported Result	Overall Risk of Bias
Chang, 2015[1313]	STARS NCT00840749	Low	Low	Low	Low	Low	Some concerns	Some concerns
	ROSEL NCT00687986	Low	Low	Low	Low	Low		
Louie, 2015[1414]	ROSEL NCT00687986	Low	Low	Low	Low	Some concerns	Low	Some concerns

Abbreviations. ROSEL=Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer; STARS=Randomized Study to Compare CyberKnife to Surgical Resection in Stage I Non-small Cell Lung Cancer.

APPENDIX D. PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	Thank you.
2	2	Yes	Thank you.
3	4	Yes	Thank you.
4	5	Yes	Thank you.
5	6	Yes	Thank you.
6	8	No - See my comments below	Thank you.
Is there any indication of bias in our synthesis of the evidence?			
7	1	No	Thank you.
8	2	No	Thank you.
9	4	No	Thank you.
10	5	No	Thank you.
11	6	No	Thank you.
12	8	No	Thank you.
Are there any published or unpublished studies that we may have overlooked?			
13	1	No	Thank you.
14	2	No	Thank you.
15	4	No	Thank you.
16	5	Yes - Lencioni et al. Lancet Oncol 2008; 9:621-628. Palussiere et al. J Cardiovasc Surg 2018; 13:91	Thanks for pointing these out. Both studies were captured by our search but excluded during title and abstract screening process since these were single arm studies without a comparison group.
17	6	No	Thank you.
18	8	No	Thank you.
Additional suggestions or comments can be provided below.			
	1	ES Key Findings; second bullet:	We revised per suggestion.

Comment #	Reviewer #	Comment	Author Response
		I'd use "patient-centered" language throughout. Suggest here " for patients with medically ...." Suggest changing throughout	
	1	ES Key Findings; fourth bullet: Not sure why you have this recommendation here, it's not a finding. If you have a recommendation for KQ1-2, why not KQ3?	The bullet refers to the findings from our evidence map and notes that cryoablation, radiofrequency ablation, microwave ablation and laser ablation were studied. We then provide “sub-bullet items” directly below to note the volume of literature and the comparisons identified. This is consistent with evidence map summaries. No change.
	1	ES Key Findings; last bullet: Fine to leave in but I don't understand why lung cancer screening is relevant here.	We left unchanged. We believe this last bullet is important for our VA partners to understand the applicability of current research for Veterans. Additionally, all the studies were conducted prior to widespread lung cancer screening. Screening alters characteristics of disease detected (*eg,* smaller and potentially less lethal cancers) and the characteristics of patients who are referred and found to have possible lung cancer. This is particularly important when discussing the potential role of treatments other than surgery as current USPSTF guidelines recommend lung cancer screening only for individuals considered candidates for surgery or willing to undergo surgery.
	1	ES Intro; page 10 line15 “ medically inoperable”: I might clarify this term. "patient's with comorbidities that place them at high-risk for severe complications during or after surgical resection for lung cancer"	Added: “(due to advanced age or with comorbidities that place them at high-risk for severe perioperative complications).”
	1	ES: Maybe this is just how you write all Summaries. But it seemed a little weird to read the whole thing and never have the KQ's spelled out.	Thanks for bringing this to our attention, the KQs have been added to our Executive Summary.
	1	ES Intro, page 10 line 26: Above you said "early", here "Stage I". I suggest being consistent and/or clarifying the difference.	Thank you for noting this. We have clarified use of the term “stage 1” when specifically addressing the studies and the key question (the population of interest is “adults with medically operable stage 1 non-small cell lung cancer.” However, in the introduction and discussion we use the broader term “early stage”, for example, we note

Comment #	Reviewer #	Comment	Author Response
			that the evaluated strategies are used for an expanded group defined as those with “early-stage lung cancer”.
	1	ES Future Research last bullet: This last bullet point and the sentence that begins, "Finally, studies..." seem outside the scope of the Systematic Review. A minor style point is why is the "FInally, studies..." sentence not w/ the bullets?	Thank you. We have added bullets to last two research items. An important part of the future research needs paragraph is to identify and highlight the identified gaps in current research in the context of our systematic review. We have left this sentence unchanged.
	1	Methods, KQ page 16 line 40: Maybe not here but do you want to explain why KQ 1-2 only included RCTs and why KQ3 was any comparative study? Why didn't you include non-RCT comparative studies in KQ1-2 or have an additional question? There might already be systematic reviews of the observational studies that would have been in KQ1-2 that you might want to cite.	Thank you. We have added rationale for our inclusion criteria and outlined the limitations of observational studies in addressing this question. We did reference one of the existing systematic reviews but did not perform a comprehensive review of reviews.
	1	Table 3 tumor stage: You might want to add a footnote for which AJCC version they used for stage	This has been added.
	1	Figure 4: Don't you still need a reference? Is a big bubble 10 people and a small one 1?	Thanks for pointing this out, more explanation was added to the figure to describe absolute sample size.
	2	The following editorial recommendations are indicated by the PDF page # P6 line 52 – I recently resigned as NODES co-director. Please changes title to: Drew Moghanaki, MD, MPH Staff Physician Co-Director Lung Precision Oncology Program VA Greater Los Angeles Healthcare System	This has been updated.
	2	P12 line 38 – consider clarifying these are “retrospective comparative studies”	This has been clarified.

Comment #	Reviewer #	Comment	Author Response
	2	P13 line 30 – consider adding (NCT02984761) after "SBRT".	Thank you, the NCT# has been included.
	2	Methods – it would help readers to define the KQs earlier in the manuscript, perhaps in the first paragraph?	Thank you. The KQs have been added to our Executive Summary.
	2	P13 line 49 – it's unclear what "dual consensus" is. Consider clarifying.	Changed to read: Any article judged to be excluded at the abstract level required confirmation by a second reviewer; articles included by either reviewer was advanced to the full-text review stage.
	2	P13 line 51 – the manuscript hasn't clarified yet who comprises the group that is resolving disagreements by consensus	Consensus included all named ESP review authors as issues of disagreement included research methods and clinical content and therefore requited discussion with the broader group.
	2	P13 line 53 – it's difficult to follow the last two sentence in this paragraph since KQs aren't yet defined at this point	Thanks for bringing this to our attention, the KQs have been added to our Executive Summary, which should help the reader.
	2	P14 line 60 – the study team isn't defined yet	Changed to read "systematic review authors".
	2	P15 line 25 – I was hoping for a conclusion of the KQ3 summary as stated for KQ1	Our conclusion from the evidence maps includes a description of the quantity and breadth of evidence for specific questions. Because the heterogeneity of the studies with respect to patient populations, interventions, and study designs, we did not pool across studies and make inferences about effect size or overall certainty of evidence.
	2	P15 line 43 – I would use the term "safety" instead of "harms"	Thank you but this has been left unchanged. Harms is standard term when referring to "complications"/adverse effects of an intervention.
	2	P15 line 54 – "are unlikely"	This has been corrected.
	2	P16 line 12 – instead of 17, please state "at least 16"	This has been corrected.
	2	P16 line 16 – the vast majority of stage I NSCLC will continue to be diagnosed incidentally, with the minority being screen-detected. Therefore, it may be better to rephrase this sentence to "Individuals eligible for VALOR and other future comparative effectiveness studies are more likely to have lung cancers detected by lung cancer screening than in previous publications."	Thank you. We have removed this sentence.

Comment #	Reviewer #	Comment	Author Response
	2	P16 line 26 – consider “randomized trial data” instead of “randomized trials”	Thank you. This has been changed.
	2	P17 line 14 – consider “treatment outcome uncertainty”	This has been changed.
	2	P23 line 34 – clarify “randomized trials”	This has been addressed.
	2	P23 line 44 – this sentence is difficult to reconcile (is it higher rates of relapse?)	We agree this is confusing. We reviewed this and believe it is most appropriate to note the difference in the follow-up intervals and not speculate on the possibility for undetected relapses.
	2	P41 line 44 – replace “17” with “at least 16”	This has been corrected.
	4	The VA Evidence Synthesis Program review of the state of evidence about Non-Surgical Therapies for Early-Stage Non-Small Cell Lung Cancer by Shahnaz Sultan and colleagues describes the current state of evidence for SABR and for other ablative therapies for NSCLC. Overall, the manuscript is very well-written and describes very well the current state of the evidence base for the 3 Key Questions. For KQ 1, they reference only the RCTs which were ended early with very low numbers because of poor accrual. This is quite poor evidence for decision-making and thus describes a situation where more well-designed studies and more evidence is needed. For KQ 2, there was not enough good evidence found to inform any answers at all. For KQ 3, 18 retrospective studies were referenced, including many different comparison arms, but no solid conclusions could be made from any of those studies. I found it unusual that they used non-randomized, retrospective studies for the ablative therapies question (KQ 3) but did not consider any of the non-randomized data for KQ 1 and 2. For those questions KQ 1 and 2, there are innumerable studies in the medical literature using non-randomized data, many which show improved outcomes with surgery as compared to SABR, and I would think some commentary on that data would be warranted. Also, I would have liked to see some sort of conclusion statement for KQ 3, based on the data reviewed, even if	Thank you for the comments. We added information to justify our different criteria for KQ1 and 2 vs. KQ3. Essentially, in consultation with our Nominating Partner and TEP members we focused on evidence from randomized controlled trials to address comparative effectiveness and harms of surgery vs. radiation therapy for Stage 1 non-small cell lung cancer in medically operable adults. This decision was based on evidence that current data from nonrandomized trials were inadequate to adequately inform clinical and policy decisions. The goal of KQ3 was subsequently refined from the original topic nomination brief to include an evidence map of all “alternative” ablative therapies used as monotherapy to treat stage I lung cancer. With an evidence map, we intentionally broadened our scope to include comparative studies that were RCTs as well as non-RCTs since the focus of an evidence map is to provide an overview of the breadth of the evidence of all comparative studies across a range of ablative therapies and outcomes reported. We did not formally rate study risk of bias, extract effect sizes or assess overall certainty of evidence. We agree that the evidence is likely very limited for “alternative ablative therapies”. There is not sufficient evidence for us to directly compare SABR with “alternative ablative therapies

Comment #	Reviewer #	Comment	Author Response
		it is the most minimal of conclusions that are able to be drawn. I say this because I find the evidence for those alternative ablative therapies to be much less strong than for SABR. I would like to see some summary conclusions stating that the outcomes are superior with SABR as well as with surgery when these retrospective comparisons are made if the authors are able to do so. I do believe that the RCT comparison of SABR to surgery is a very worthwhile pursuit, whereas those other ablative therapies do not have as much promise and do not warrant large RCTs in operable patients. And I do not think most surgeons who treat lung cancer would have equipoise for such an RCT. But I can understand that the authors did not feel the evidence warranted much in the way of conclusions. Overall, I think the authors did a tremendous job of describing the current state of the literature on these topics. But the current state leaves many unanswered questions and thus points to further research needs.	We have further highlighted the limited quality (based on study design (mostly administrative data sets); country of origin, interventions and comparisons and outcomes of interest.). Such reporting can highlight gaps in research evidence. We thank the reviewer for the statement of our overall work. We agree that the current evidence has many gaps and requires future research. We agree that RCT are needed (especially in screen detected lung cancer) and provide this as recommended future research. We summarize some suggested future research to close those gaps.
	5	Although I believe the conclusions of the report are accurate, it discounts so much data because of the narrowness of the criteria to answer the questions, making most studies ineligible. With few randomized trials to include, it is expected that this report has little to ultimately conclude, most of which was obvious. As such, this report feels a bit hollow; in that, there is no information of the current status, benefits, outcomes and usefulness of any ablation modality, for instance, despite 3 trials, database studies, etc. to be useful. If the VA waits for or conducts a randomized trial, that would be great, but what therapies can be offered until this occurs - this report sheds no light. If a trial is to be conducted, it should have 3 arms with thermal ablation included, so that we can understand where and how each modality (surgery, SBRT, ablation) fits into the treatment paradigm and which patient and which tumor location would be appropriate for each of the local therapies.	We appreciate the concerns of this reviewer. Based on discussion with our Nominating Partner and TEP members the viewpoint was that a review that included information from non-RCT would not adequately inform clinical practice and policy and that prior reviews had not resolved that issue. Excluding a large body of data is justified because it is likely to be biased and provide inaccurate information that could wrongly guide clinical decisions and impede needed research. Thus, one is left with very little data to guide clinical decision making…that in and of itself can be viewed as a very important “take home message” including the importance of completing RCTs that address the issue. We thank the reviewer for the suggestion on a three-arm trial. We have included this in our future research need.
	6	Thank you for the opportunity to evaluate this report.	This has been corrected for consistency.

Comment #	Reviewer #	Comment	Author Response
		As a small typo the wording of KQ2 is different on pages 16 and 20	
	6	Overall, there are three significant limitations. 1. It is not clear why KQ1 and KQ2 were limited to RCTs but KQ3 was not. There are certainly biases present when comparing ablative therapies to either surgery or radiation, so the question arises of why include observational studies with KQ3 but not the other two key questions. There have been attempts with retrospective cohorts to compare SBRT and surgery, why not include the data from these studies with the caveats that go along with these types of investigations and the discussion of the associated risks of bias and certainty of evidence. The shortcomings of retrospective studies would emphasize the need for RCTs in this space but provide the best evidence we currently have.	Please see our points discuss above.
	6	2. As I interpret KQ2 (on page 16) wouldn't the prospective studies limited to either SBRT or surgery for early-stage NSCLC address this question. For example, a RCT of SBRT vs surgery is not needed to address the benefits and harms of "surgery characteristics (type of surgery [minimally invasive vs. open])" or "SBRT characteristics (eg, dose, fractionation)". It is likely that any SBRT vs surgery RCT will be underpowered to address these questions anyway. Along these lines, the VALOR study does not allow for single fraction SBRT, but there are studies RCT of single fraction SBRT that address this topic. A thoughtful analysis of the benefits and harms elucidated by trials of either modality may indicate those patients which may be better served by an alternate approach and set the stage for prospective studies.	We thank the reviewer for this comment. KQ2 specifically focuses on whether the effectiveness and harms of SBRT or surgery vary by these characteristics, essentially subgroup findings or effect modification. Use of non-RCTs would be limited in a similar fashion for KQ2 as for KQ1
	6	3. The "quantity and characteristics" of studies addressing ablative techniques are well summarized in the results of KQ3 but it is unclear why this KQ was limited to this "meta" question. Reading through the manuscript I expected a full discussion of the findings of these studies, again with discussion of the caveats of the	We thank the reviewer for this. As noted previously the intent of KQ3 was to provide an evidence map summarizing the state of the literature according to intervention/comparison, study type and outcomes reported rather than effect size estimates or directionality. As with KQ1 and 2 the current evidence base for KQ3

Comment #	Reviewer #	Comment	Author Response
		observational studies that I presume were included. In summary, this ESP report provides an in-depth evaluation of one, underpowered analysis of two prematurely terminated RCTs. Serious thought should be given to expanding KQ1 to include observational studies, KQ2 to include prospective studies addressing SBRT or surgery individually, and a complete discussion of the results of studies identified for KQ3.	would necessarily be very limited in number and poor in quality as almost all reports were observational and frequently from administrative data (sometimes using overlapping data systems). Our ESP review team worked in consultation with our Nominating Partner and TEP members to determine study inclusion criteria. As noted previously, inclusion of findings from nonrandomized trials was deemed inadequate to accurately inform clinical decision making and could impede future RCTs if the perception was that non-RCT could sufficiently address. We did highlight one non-RCT in the discussion section and note the serious methodologic limitations in this widely cited report and thus the inability of non-RCTs to adequately resolve treatment uncertainty.
	8	Thank you for the opportunity to review this manuscript. The authors have assembled the data available for assessing the use of ablative therapies for early-stage non-small cell lung cancer. The manuscript is well written and the data clearly presented. However, I think there a few aspects that could improve the evidence synthesis. These points are detailed below. 1. The Key questions missing from the executive summary and do not appear in the manuscript until page 16 (19 in the pdf) although they are mentioned throughout the executive summary. I would recommend adding the key questions to the key findings box.	Thanks for bringing this to our attention, the KQs have been added to our Executive Summary.
	8	2. Table 3. Data in the STARS trial is listed in the table as NR, although was apparently available to the authors of the Chang publication (#13 in the references). It would be helpful to the reader if that missing STARS data was extracted from the Chang publication and then footnoted regarding the way it was determined (not from the primary investigators, but via the Change publication). This would make it easier for the reader to compare the populations of the STARS and ROSEL trials directly.	Thank you for the suggestion, however, the Chang publication did not report results separately by trial, so this information was not available to review authors. Review authors did attempt to contact the trial investigators of the STARS study for this data but were unsuccessful.

Comment #	Reviewer #	Comment	Author Response
	8	3. Table 5. The SABR and Surgery columns are reversed	Thank you for bringing this to our attention, this has been corrected.
	8	4. I wonder if the decision to use evidence mapping for key question 3 was the right one. As someone who may be interested in seeking out an evidence synthesis like the one presented here, I would be most interested in seeing what the outcomes of the accumulated data was. I recognize the limitations associated with the retrospective and/or observational data presented in the selected publications, as well as the value of the summary data that was presented. Nevertheless, I think a brief summary of the outcomes, perhaps limited to just the studies from the larger database publications, and with the appropriate qualifications around how to interpret this data, would be very valuable. Alternatively, if the authors feel strongly about not including outcome data from the studies for key question 3 there should be a statement in the methods section for key question 3 similar to this statement from the limitations section: “we also did not provide information on effect size, direction of effect, or assessment of quality of studies to limit misinterpretation or over reliance of these studies for decision-making”, to alert the reader to the limited nature of the evidence mapping.	Thank you. We note previously our rationale for conducting an evidence map.