Nr	commenting institution	Page number* (or 0)	Section number	Line number* (or range)	Comment and suggestion for rewording* *(Please insert each new comment in a new row)*	Character of comment * ('major' | 'minor' | 'linguistic')	Implementation Comments
1	RIZIV	16	2.2.3.	332	We suggest to add the following reference at the end of the phrase: Glasziou P et al. Reducing waste from incomplete or unusable reports of biomedical research. The Lancet 2014;383:267-276	minor	Reference added
2	RIZIV	16	2.2.3.	336-337	There is no reason why this important statement and the references 41-43 should stay between brackets < remove brackets	minor	Suggestion implemented
3	Ecker & Ecker	General comment			Ecker + Ecker GmbH, a healthcare consultancy based in Germany with strong expertise in the early benefit assessment, is welcoming the effort by the EUnetHTA to provide a framework that allows for a structured and evidence-focused HTA process. The development and constant evaluation of the according methodology is key for a standardized and unbiased development of HTA documents.		
4	Ecker & Ecker				The "Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness" document, as of August 2019 in version 2.0, is an essential guideline that meets the criteria for a systematic research process, leading to the identification of the accessible information in its entirety and thus allowing the evidence-based assessment of the identified data set.		
5	Ecker & Ecker				While the guideline in its current form is of high quality in general, we identified several aspects that should be addressed before the finalized version 2.0 is published. They are described in detail below.		
6	Ecker & Ecker	29	3.4.1	825-828	In line 825 ff., the guideline is citing the "European Medicines Agency – Clinical data" website as an appropriate source for regulatory documents including clinical study reports. While this may be the case in general, the publication of new clinical data is currently suspended due to the relocation of the agency to the Netherlands. No date has yet been communicated by when the EMA will resume the publication of new clinical data. Therefore, the website in its current state is not a reliable source for regulatory documents and should be treated as such. We propose the following wording instead (changes highlighted in red): "In addition, EMA introduced Policy 0070 on data transparency, which became effective in October 2016 [197,198]. Regulatory documents, including CSRs on all drugs submitted for approval, have since been available on the Agency´s website "European Medicines Agency – Clinical data" [199]. However, publication of clinical data is temporarily suspended and the database is currently not up to date."	major	Text adapted
7	Ecker & Ecker	24	3.2.1	647	For tables, captions should be placed above the table, not below. In general, the formatting of the tables in the document is not consistent. Most of the tables are not numbered. Some headings are bold, some are not. One table features a gray background, the others do not. A consistent formatting increases readability and orientation within the document.	linguistic	Thank you for pointing that out. We labeled the tables uniformly.
8	Ecker & Ecker	45	Annexe 1	1437	Reference 148 is flawed. The cited link to the German Clinical Trials Register is invalid. Instead, the following URL should be cited: https://www.drks.de/drks_web/ Furthermore, the DRKS is now associated with the German Institute of Medical Documentation and Information (DIMDI), not the University of Freiburg.	minor	Thank you for pointing that out. We have updated the reference
9	EFPIA	0			The document outlines some of the best-practice approaches for SLRs, and whilst this represents a good foundation, the document does not recognise that some best practice is unlikely to be fully realised given the particular limiatations and challenges that will face researchers in the assessment of medicines at the time of regulatory approval. Some pragmatism is therefore required as undertaking SLRs in the timeframes envisaged by the REA/JCA will limit scope for SLR authors to meet these standards. For example, it may be difficult to source unpublished data from authors of papers in the timeframes envisioned, and industry researchers may struggle to gain access to other companies' data as the requst may be seen as commercially oriented. This guidance document should therefore explicitly recognise the pragmatism that may be required for reviewers of SLRs conducted to support REA/JCA, and REA/JCA authors should therefore not be mistaken in considering an SLR submission as incomplete where circumstances prohibit the SLR authors from following the full guideline in every aspect		The guideline provides the current knowledge in the field of information retrieval for conducting SR / HTA. For this purpose, a systematic search is conducted in several databases as well as in other information sources is needed. "Pragmatism" cannot lead to data being collected unsystematically and incompletely. --> No changes to text
10	EFPIA	0			Who are the recipients of this guideline? If those are EUnetHTA members, should manufacturers and sponsors align with this guideline?	Major	The recipients of the guideline are listed under 1.1 (lines 225-227): "In particular, the requirements presented in this methodological guideline aim to provide orientation for systematic searches on clinical effectiveness conducted within the framework of EUnetHTA." When manufacturers prepare reports under EUnetHTA, the requirements of this guideline, as well as specifications in the respective templates need to be considered. --> No changes to text
11	EFPIA	0			During the guideline review, a gap was identified between the proposed methodology with this that could be implemented by pharmaceutical and medical devices companies on several aspects: 1) Question research refinement; 2) PICOS-T development; 3) Databases access; 4) Type of publications to consider	Major	We do not see any significant differences between the information retrieval according to drugs and medical devices. If we have identified differences, these are stated in the guideline. --> No changes to text
12	EFPIA	0			We think the earlier scientific dialogues with industry developers could be of mutual benefit and facilitate both , efficiency of R&D and HTA processes.	Major	Whether a dialogues with industry developers takes place is not subject of this methodological guideline. --> No changes to text
13	EFPIA	0			The whole documented is Medline/PubMed and Ovid oriented whereas EMBASE is a major actor of the information retrieval; would using sources other than OVID be seen as weaker?	Major	In Section 1.1.9 the guideline explains that there are different interfaces for a search in bibliographic databases. --> Change: Rewording in line 432
14	EFPIA	0			Given retrieval information workload, validated questions and PICOS-T is a prerequisite before developing and conducting the search queries.	Major	The guideline refers to this aspect in section 3.1.3 --> No changes to text
15	EFPIA	0			The term SRs is used for both, systematic reviews and HTAs on clinical effectiveness, although some recommendations seem only to be relevant for systematic reviews. Therefore, it would be useful to differentiate between reviews and HTAs in the document.	Major	Compared to SR, HTA includes additional domains. With regard to the provision of information on the other domains, please see line 249-256 In addition, the assessment of a submission file is not covered by this guideline . The assessment of a submission file is not covered by this guideline, please see line 261-263 --> Section 1.1 explains in more detail, now what content is excluded from the guideline
16	EFPIA	0			Time frame / Time horizon of the searches should be reasonable and take into consideration current clinical guidelines. Searches from inception do not seem reasonable as they are not taking into account medical progress.	Major	Please see comment 9 for explanation. The search should usually not limited to specific years --> No changes to text
17	EFPIA	1			Title: definition of effectiveness should be developed. The most accurate term is probably 'efficacy' as the term effectiveness can be used for evidence other than RCTs. Some are considering effectiveness only when the evidence is obtained from real world data.	Minor	The guideline refers to clinical effectiveness. For definition please see "assessment FAQ" (https://www.eunethta.eu/services/submission-guidelines/submissions-faq/) --> No changes to text
18	EFPIA	5		76	SR is insufficient and the term SLR (systematic literature review) could be added as this term is also frequently used. In addition the acronym of CENTRAL is missing and stands for: Cochrane Central Register of Controlled Trials	Minor	The abbreviation SR is widely used. --> No changes to text Acronym of CENTRAL was added on page 5
19	EFPIA	6		78-189	Definitions of HTA and SLR are missing. In addition terms like STA (single technology appraisal) and MTA (multiple technology appraisal) could be defined.	Minor	Explanations can be found here: - https://www.eunethta.eu/services/submission-guidelines/submissions-faq/ - https://www.eunethta.eu/wp-content/uploads/2018/01/Therapeutic-medical-devices_Guideline_Final-Nov-2015.pdf --> No changes to text
20	EFPIA	6			A sub-section related to the definition of grey literature could be added. "Grey literature stands for manifold document types produced on all levels of government, academics, business and industry in print and electronic formats that are protected by intellectual property rights, of sufficient quality to be collected and preserved by libraries and institutional repositories, but not controlled by commercial publishers; i.e. where publishing is not the primary activity of the producing body." (The Twelfth International Conference on Grey Literature in Prague in 2010)	Major	The guideline contains sections on grey literature, please see section 3.4.1, 3.4.4 and 3.4.5 --> No changes to text

21	EFPIA	6			A sub-section related to the definition of available primary/secondary/tertiary publications could be added.	Major	In our opinion the term "primary study" needs no further explanation. "secondary", "tertiary" --> these terms are not mentioned in the guideline --> No changes to text
22	EFPIA	7	1.1.6.	116	Embase segment is lacking. The whole publication is oriented to PubMed and Ovid (Embase), while the Embase segment can be developed by its own. Database users can contract directly with Embase without using Ovid as a search platform. Reading these guidelines, users could understood a mandatory incitement to buy Ovid access. Based on this, a new segment discussing on the difference on Embase and PubMed databases should be needed.	Major	1.1.6 explains the different PubMed segments. There is no need to explain the Embase content. In terms of choosing databases please see 3.1.4 "choosing information sources" --> no changes to text
23	EFPIA	7	1.1.6.	120	PMC is not defined	Minor	Abbreviation added on page 5
24	EFPIA	8	1.1.8.	138	ADJ for Ovid is missing. NEAR and NEXT are missing for Embase. The utility and use of proximity operators could be argued. The Boolean operators "AND" could be sufficient when searching in the titles and abstracts.	Minor	Section 1.1.8 explains the terms without specifying when certain search functions are best used. In this section also information on the approximate operators is provided. --> No changes to the text
25	EFPIA	8	1.1.8.	150-152	The function 'Emtree' in Embase is providing synonymous terms that could complete the FACET (family words)	Minor	The search lines 150-152 refer to "Search fields" --> No changes to the text
26	EFPIA	8	Summary	160-161	A major difference is also that the interfaces differ in the search syntax (it is mentioned in the text later, but could be added here)	Minor	This is what is meant by the word "functionalities". --> No changes to text
27	EFPIA	8	1.1.10.	175	CENTRAL is the 'acronym' (even if it is not a strict acronym) of Cochrane Central Register of Controlled Trials	Minor	Thank you, we added the Acronym on page 5
28	EFPIA	8	1.1.10.	171-175	As MeSH is used for PubMed, Embase has its own headings and should be developed.	Minor	please see section 1.1.10. --> No changes to text
29	EFPIA	8	1.1.10.	165-180	Author key words are not mentioned and it is central in Embase	Minor	Since authors' keywords are not controlled keywords, we do not go into them further in the guideline. --> No changes to text
30	EFPIA	10		191-200	It is stated that SRs need to be performed in a systematic, transparent and reproductible manner. However this guideline is providing only Medline/PubMed and Ovid guidance to EUnetHTA framework, as pharmaceutical and medical devices companies and other can use Embase without using Ovid platform, is this an incitement to companies or other institutions to buy Ovid? In order to obtain complete alignment when conducting an HTA, identical database languages should be necessary between the HTA bodies and companies. Why the EUnetHTA framework members wouldn't prefer Embase access instead of Ovid?	Major	The Guideline does not demand a particular provider. --> We have adapted section 1.1.9 and other sections to make this aspect clearer.
31	EFPIA	10	Summary	198-200	Will the guideline transferred to EU HTA process in the future as it is (after 2020 or when the new law is effective)?	Major	The guideline is for EUnetHTA. The use in a different context must be decided elsewhere. --> No changes to text
32	EFPIA	10	Summary	198-200	"...guideline for systematic searches (...) conducted within the framework of EUnetHTA." Should this not be a more general approach going beyond EUnetHTA?	Minor	The guideline is for EUnetHTA. The use in a different context must be decided elsewhere. --> No changes to text
33	EFPIA	10	Summary	207	General question (here and elsewhere): How are "specialists" defined and selected? There should be a documented process for this.	Major	In EUnetHTA, the requirements are as followed: • Confirmation by the HTA agency that the person proposed works as an information specialist AND • has experience in developing search strategies and conducting searches for HTAs, systematic reviews and/or other evidence syntheses. (An information specialist with little experience may conduct searches, provided that the information retrieval process is closely supervised and quality assured by an experienced information specialist.) If possible, the HTA agency should provide a list of references where the information specialist is listed as a co-author or contributor. --> Content added to Annexe 4
34	EFPIA	10/11	Summary and table with main recommendations	Table	Recommendations for registry searches are not included in the table but only recommendations for searches in bibliographic databases although in section 3.2 detailed recommendations for registry searches are given	Major	The search in study registers is represented in the 2nd recommendation. --> No changes to text
35	EFPIA	10		211-212	1st recommendation should be as follows: When conducting SRs and HTAs, the quality of the initial question is an essential condition. A well-articulated research question will provide the investigators with critical information about the project by defining the focus of the research, its scope, and the objectives. Identification, selection of pertinent information and adoption of pertinent statistical methods are also essential	Major	Not all recommendations of the guideline can be listed in the summary. However, there is a section in the guideline on "structuring the search strategy" (3.1.3). The introduction of statistical methods is not part of the guideline. --> No changes to text
36	EFPIA	10		211-212	Current 3rd recommendation: Instead of "Besides MEDLINE, other bibliographic databases such as Embase and CENTRAL should be searched to identify all published relevant studies on the topic of interest", this sentence could be replaced by "MedLine, Embase and Central should be searched to identify all published relevant studies on the topic of interest"	Linguistic	In the methodological guideline, we review the existing literature on the topic. Concrete instructions can be found in Appendix 4. --> No changes to text
37	EFPIA	11		211-212	Current 4th recommendation: Instead of "Individual search strategies must be developed for selected databases using both free-text terms and, if available, subject headings", this sentence could be replaced by "Individual search strategies must be developed for selected databases using either free-text terms or limitations to title/abstract, according to the research field (e.g. diabetes terms in title or abstract) and, if available, subject headings.	Linguistic	The content of the proposed text does not differ from that of the guideline. --> No changes to text
38	EFPIA	11		211-212	Proposed new recommendation: Question to be raised: are several PICOS-T to be developed because of several populations and/or comparators for a given intervention? A SR/HTA could frequently consider this kind of situation. In this case, a global search strategy wouldn't facilitate the selection of papers by investigators.	Major	--> In Section 3.1.3 we have added a reference to different PICOS and comment in more detail on this topic.
39	EFPIA	11		211-212	Current 6th recommendation: The database access dates should be clearly showed. Then, during updates, an overlap of 2 months is needed when performing the search compared to the previous one (e.g. initial search performed in July 2015, the update should consider a time frame from May 2015). The reason is that databases are being retroactively updated and new added papers the at the time of the initial search could be miss.	Major	Please see section 3.1.10 for details of an updating searches --> No changes to text
40	EFPIA	11		211-212	Current 7th recommendation: This recommendation is not clear for the reader. Agencies are also conducting rapid reviews using systematic literature reviews. The term of 'rapid review' should be added to the guideline in order to help the reader making the difference between this kind of reviews and more classical reviews using primary papers.	Major	Rapid Reviews are not part of this guideline. --> We have reworded the sentence in the recommendations.
41	EFPIA	10	Summary	211	7th recommendation: the update search should have a sufficient timely overlap.	Major	See comment number 39 --> No changes to text
42	EFPIA	12			A PICOS-T sub-section could be developed as this is the corner stone and the canvas of the search strategy. On the other hand, we suggest to expand the PICOS to PICOS-T in order to take into consideration the Time frame / time horizon of the search. In addition, a product can be labelled in different populations. So according to the population label, the comparators and time frame / Time horizon of the search could differ. Also complete and clear list of exclusion / inclusion criteria can help the investigator with the step of papers selection.	Major	please see comment nr. 38
43	EFPIA	12	1,1	218-222	Similar tools will ensure alignment between EUnetHTA framework members and manufacturers. In practice, the manufacturers are submitting their own dossiers using the tools they have access to. The companies could have direct access to Embase without using Ovid. As previously stated, the search language is not the same between both databases.	Major	please see comment nr. 13, 30
44	EFPIA	12	1,1	214-227	When conducting SRs and HTAs, the quality of the initial question is crucial for information retrieval. A well-articulated research question will provide the investigators with critical information about the project by defining the focus of the research, its scope, and the objectives.	Major	This aspect is covered in section "3.1.3. Structuring the search strategy". --> No changes to text
45	EFPIA	12	1,1	225-227	There is a difference between 'clinical effectiveness' and 'clinical efficacy', and this guideline should be careful in use of either phrase in isolation.	Minor	please see comment nr. 17

46	EFPIA	12	1,1	229-236	When assessing the relative efficacy assessment (REA), abstracts from congress and conferences are currently being included as they could be the unique source of information available by the time of the assessment. Then a paragraph on the topic could be developed. But the reader should be informed that the information coming from conference/congress abstracts could differ from full paper publication. In practice: 1) Abstracts from Congresses/Conferences are the main source of information when a full publication is not yet available. 2) Since a full publication is available, it will become the main source of information not the abstract any more. 3) In case efficacy data are published by regulatory or reimbursement HTA agencies, these data will be preferred over full paper publication. In conclusion, the assessment HTA efficacy data is preferred over full publication and full publications is preferred over abstracts	Major	In the guideline there is a section on searching for conference abstracts (please see 3.4.4). --> No changes to text
47	EFPIA	12	1.1	249-251	"The description of searches for studies on specific aspects such as safety, diagnostic accuracy, and economic evaluations (for HTAs) will not form part of this guideline.". But this would be helpful. A reproduction of search guidance for clinical evidence is nice, but not really neccessary. Respective processes are well established. So this is just another guidance summarizing well known facts. Just adding more bureaucracy.	Major	In the guideline we refer to the SuRe info portal (http://vortal.htai.org) for these other aspects. --> No changes to text
48	EFPIA	15	2,1	270-289	Embase segment is lacking. The whole publication is oriented to PubMed and Ovid (Embase), while the Embase segment can be developed by its own. Database users can contract directly with Embase without using Ovid as a search platform. Reading these guidelines, users could understood an mandatory incitement to buy Ovid access. Based on this, a new segment discussing on the difference on Embase and PubMed databases should be needed.	Major	please see comments nr. 13, 30
49	EFPIA	15	2.1	272	How were those sources selected? A systematic search would require a description (e.g. timliness, topic, region)	Minor	The methodological approach of the guideline was described and agreed on in advance in a concept paper. --> No changes to text
50	EFPIA	15	2,1	288	The related citation search also exists in Embase. However it is less accurate than in PubMed.	Minor	The commentary refers to the methodology used to produce this guideline. The authors of this guideline have applied the Pubmed´s related citation search. A general description of the similar articles function can be found in section 1.1.4. --> No changes to text
51	EFPIA	15	2.1	293-5	It is not explained how "relevant sections" are defined or how they are identified; no documention of inclusion/exclusion criteria/reasons	Minor	please see comment nr 49
52	EFPIA	15	2	271-353	Section 2 is confusing as this is not clear enough for the reader. Is this section related to the conduction of the guideline on the information retrieval or to the conduction of SRs/HTAs? In addition, was there a protocol for the development of this guideline? If this issue is not related to the development of the guideline, the research question and the PICOS-T framework should be completely detailed in the first sections of the protocol.	Major	It is stated that the section 2.1 refers to the methodology used to produce this guideline. --> No changes to text
53	EFPIA	15	2.1	282-6	a) Consider adding the German “Manual zur Literaturrecherche für Leitlinien”, ed. German Cochrane Centre et al. b) Is the selection of sources quality-checked or arbitrary? If the former, this should be stated in the text.	Minor linguistic	Please see comment 49
54	EFPIA	15	2.1	293-5	The 2nd author should also check the unextracted sections for overlooked parts with pertinence	Minor	Here we describe the applied methodology. --> No changes to text
55	EFPIA	15	2.1	293-5	It is not explained how "relevant sections" are defined or how they are identified; no documention of inclusion/exclusion criteria/reasons	Minor	Please see comment 49
56	EFPIA	15	2.2	305-306	How is an "information specialist" defined? This intends to raise hurdles for companies to search on their own als - assumed with high probability of being true - of course only EUnetHTA staff will be sufficiently specialized.	Major	please see comment nr. 33
57	EFPIA	16	2.2.2	312-315	Information specialists should also be responsible for proper de-duplication of search results from multiple databases as this process can also be complex	Minor	This is a summary of the main tasks. However, we discuss this step in Section 3.1.7. --> No changes to text
58	EFPIA	16	2.2.2	316	How are the “specialists” selected?	Minor	please see comment nr. 33
59	EFPIA	16	2.2.3	333-334	In addition to using information from study registries to verify published data, another potential source is published trial protocols.	Minor	Publications of clinical trials are sometimes supplemented by study protocols, which are also a relevant source of information. In general supplements to publications should always be regarded as part of the publication itself. --> no changes to text
60	EFPIA	16	2.2.3.	335-337	Usually in PRISMA diagram flow of SLRs, the number of publications is higher than the number of studies. Even if it is not recommended to publish several times a study, this occurs frequently.	Minor	--> We have adapted the text accordingly
61	EFPIA	16	2.2.4	345-51	1) CSRs are normally not published officially and, thus, not searchable systematically in any case 2) this is not made clear in this passage but in section 3.3; a short sentence with reference to section 3.3 should be added	Major	1) Please see section 3.4.1 2) Section 2.2.4 deals with the matching of documents and data. A reference to 3.3. is therefore not useful. --> No changes to text
62	EFPIA	17	3	354-358	Before starting any search, the information specialists should confirm the research question, the objectives and the PICOS-T are developed and validated into a protocol.	Major	These aspects are already covered in sections 2.2.1 and 3.1.3 --> No changes to text
63	EFPIA	17	3.1.1	Figure 1	This is one way of conducting the searches and generally adhered to by researchers. However, it is very dominant and strict. No need to "press checklist" or to "Import into screening tools" in every case. One can do it, but this must not be set als mandatory.	Major	In Figure 1 we have summarized what is described in more detail in the following chapters. --> We have adapted the introductory text.
64	EFPIA	17	3.1.1.	363-364	Giving to the workload of this kind of projects, additional boxes in the figure 1 could be implemented with the confirmation of the research question and objectives by investigators.	Major	The flowchart is a brief summary of the bibliographic search. --> No changes to text
65	EFPIA	17	3.1.1.	363-365	The current figure 1 is adapted to guidelines development by a HTA body when assessing several products and several therapeutic classes. In this case, conducting a preliminary search is mandatory. This figure is not appropriate for the case of the assessment of one product submitted by manufacturers (Single Technology Appraisal: STA) or the assessment of several products in late phase development belonging to the same therapeutic class (multiple technology appraisal: MTA). In case of STA or MTA, the direct clinical evidence as well as the evidence generated for the Relative Efficacy Assessment (REA) through indirect comparisons are being submitted by the companies themselves. So, the question search, the objectives and the PICOS-T could be easily developed by using the materials provided by the companies and the search strategy developed accordingly. Usually this evidence is taking into consideration the evidence provided by the clinical development program and comparators, outcomes of interest defined by current clinical guidelines. So, the box (structuring the search strategy) is incomplete as only facets 1 (population), 2 (intervention) and 3 (study type) are described, the outcomes should be part also of the facets. A figure 2 could be developed by taking into considering these thoughts on STA/MTA. Within this new figure the box (structuring the search strategy) will become: facets 1 -population; Facet 2 - intervention; Facet 3- Comparators; Facet 4- Outcomes; Facet 5 - Study design; Facet 6- Time-Frame/Time Horizon. If any preliminary search this should consider current guidelines and an HTA review in order to precisely know where is the positioning of a new product: first line, second line, third line etc.	Major	a) Under 1.1 the following aspect is referred to in the section "excluded aspects": "The assessment of a submission file is not covered by this guideline. Detailed information on the procedure can be found in the internal EUnetHTA standard operating procedure (SOP) “PT-03-InfRetr””. b) As described in section 3.1.3: Outcomes are usually not included in a systematic search, as they are generally inadequately reported in abstracts of journal publications (line 402-403). We do not see any necessity to create another flowchart. Please see comment 38 in terms of several populations or interventions. --> No change made to the guideline

66	EFPIA	17	3.1.1.	363-366	The figures can be restructured and follow a more coherent order. 1) First box confirming the questions and objectives, 2) Structuring the search strategy (PICOS-T) 3) Selecting databases. This should take into consideration what are the access rights to the databases. Medline/PubMed and CENTRAL are public databases but not Embase. The investigators can have or not access to search platforms like Ovid. If the investigators had contracted with Elservier for Embase access, the investigators can decide to use Embase search engine as the platform allowing to explore PubMed or Embase. When access to Embase is possible, we recommend to develop search strategies specific to Embase, but also to PubMed and consult the databases separately: PubMed in one side and Embase in the other side. When using Embase as search engine for exploring PubMed, we noticed some differences when compared to results issued from direct consultations using PubMed as engine search in MedLine. 4) Identifying free-text terms 5) Adapting the search syntax 6) ...	Major	The flowchart contains all the mentioned aspects; details can be found in the following sections. In terms of Embase please see comment 30. --> No changes to flowchart
67	EFPIA	18	3.1.2.	366-375	To adapted according to page 17 comments	Major	From our point of view, no adjustment is necessary here.
68	EFPIA	18	3.1.2	367-369	It is not clear whether involvement of an information specialist at this early stage of preliminary searching is necessary, or preliminary searches are something authors/investigators can and should perform themselves in order to facilitate formulation of the actual search strategy. Some clarification here would be good.	Minor	We leave this explicitly open and leave it to the author teams --> No changes to text
69	EFPIA	18	3.1.2.	383	Embase is also providing access to 'similar records'	Minor	We have adapted the text
70	EFPIA	18	3.1.2	387-90	A high-quality review may also overlook relevant evidence, so SRs should be double-checked for comprehensive evidence consideration regardless of their "quality" (however that may be defined)	Linguistic	In this chapter we describe the execution of a preliminary search. --> No changes to text
71	EFPIA	18	3.1.2.	387-390	For preliminary searches, structured searches including Boolean terms can be developed using Google until limitation 200 characters	Major	We do not agree that a search for reviews should be performed in Google. see Holone 2016 (PMID: 27374832) --> No changes to text
72	EFPIA	18	3.1.3.	393 - 397	The term 'C' in the PICOS-T refers to Comparators instead of Comparisons PICOS term could be extended to PICOS-T in order to take into consideration the Time Frame / Time Horizon	Minor	The C in PICO can stand for Comparator as well as Comparison. Since a search is not restricted to a specific time period by default, T should not be used by default. --> No changes to text
73	EFPIA	18	3.1.3.	401-406	The search strategy should be closer as possible with validated PICOS-T. In dossier submitted by companies, the outcomes are being clearly specified and could benefit from previous discussions with HTA agencies. Outcomes are currently being searched in all available publications: abstracts from congresses/conferences, full paper publications and evidence made available by HTA agencies. The decisions on how the evidence can be used is based on feasibility study for Indirect Comparisons (ITCs) where the amount of evidence is in depth studied in order to judge of potential comparisons through common nodes (comparators)	Major	As stated in chapter 3.1.3. only the most relevant concepts of PICOS should be used for the development of a search strategy. For example a recently published study shows, that "outcomes" are often not mentioned in the abstract of a reference. Therefore, the search should not be restricted to outcomes. --> No changes to text
74	EFPIA	18 - 19	3.1.3.	407-414	This section is not clear enough for readers. Search strategies are using the Theory of sets where parent terms are combined using Boolean operator 'OR', where the intersection between family words is using 'AND'.	Major	We've adjusted the text.
75	EFPIA	19	3.1.3	409-412	The same term in different variations should be grouped in one line to increase readability. E.g. drug codes: "XY-0815 OR XY 0815 OR XY0815"	Minor	No changes to text
76	EFPIA	19		415-418	In terms of the filters for the searches, it seems the recommendation is not to limit the search by language, nor publication year. This could be problematic in terms of number of hits and review of the titles/abstracts in foreign languages. It may not be reasonable to assume that manufacturers should consider articles in all languages.		In Section 3.1.3 we point out that if the search strategy contains, for example, a language or year restriction, these must be described in the inclusion and exclusion criteria. --> We adapted the text in Annexe 4
77	EFPIA	19	3.1.4	421-441	Embase segment is lacking. The whole publication is oriented to PubMed and Ovid (Embase), while the Embase segment can be developed by its own. Database users can contract directly with Embase without using Ovid as a search platform. Reading these guidelines, users could understood an mandatory incitement to buy Ovid access. Based on this, a new segment discussing on the difference on Embase and PubMed databases should be needed.	Major	please see comment nr. 13 and 30
78	EFPIA	19	3.1.4	421	As comments for figures, this subsection could be moved	Major	From our point of view, the chapter is correctly placed here. --> No changes to text
79	EFPIA	19	3.1.4	421-39	The necessity of employing searches in more obscure sources heavily depends on the subject. Someone therapeutic areas are notoriously underrepresented in ‚major' databases	Minor	No changes to text
80	EFPIA	19	3.1.4	428	Central could be confused with PubMed Central, therefore it would be good to mention that Cochrane´s Central is meant	Minor	We have added CENTRAL in the section Acronyms - Abbreviations
81	EFPIA	19	3.1.4	426-430	The Cochrane Systematic Review Database may be recommended for the search for published SRs.	Minor	Section 3.1.4 describes the search for ***primary*** studies. --> No changes to text
82	EFPIA	19	3.1.4.	421-430	As previously stated, Embase segment is lacking. The whole publication is oriented to PubMed and Ovid (Embase), while the Embase segment can be developed by its own. Database users can contract directly with Embase without using Ovid as a search platform. Reading these guidelines, users could understood an mandatory incitement to buy Ovid access.	Major	pease see comment nr. 13 and 30
83	EFPIA	19	3.1.4	431-432	Why referring to Ovid only? There are also other meta-search platforms. Sounds like only OVID will be accepted.	Minor	pease see comment nr. 13 and 30
84	EFPIA	19	3.1.5.1	444-445	The part in brackets/publication type should be clarified: what is meant exactly with publication type and why was this added in brackets	Minor	we have added "Publicaton type" in section 1.1.10
85	EFPIA	19	3.1.5.1	447	Maybe it could useful for the reader to know 'free text terms' is referring to title and abstracts but not to the body text. This can be an issue in case of data scarcity for a condition where sensitivity should be preferred to specificity.	Major	Please see explanation in section 1.1.10. --> No changes to text
86	EFPIA	19	3.1.5.1	447	The function 'Emtree' in Embase is providing synonymous terms that could complete the FACET (family words)	Minor	We have added Emtree as a further source for the identification of search terms.
87	EFPIA	20		475-477	The authors refer to clinical effectiveness. However, the vast majority of the document focuses on retrieving RCT (efficacy) data, there is very little info on retrieving/using RW data (effectiveness)	Major	The guideline deals with clincial effectivness. The proposed distinction between efficacy (=RCT) and effectiveness (=non-RCT) is not correct. The extent to which so-called real-world data can contribute to the assessment of relative effectiveness is open and not part of this guideline. --> No changes to text
88	EFPIA	20	3.1.5.1	462	That is one example for provision of just another guidance. "...should be summarized with the èxplode˙function, if meaningful." That is common knowledge. It would be of greater relevance to provide kind of an algorithm or guidance on WHEN it is meaningful.	Major	We specifically address this issue by providing an example in annexe 3. --> No changes to text
89	EFPIA	20	3.1.5.1	467-480	Why not include a list of filters including empirical evidence based on their utilizazion AND a description of their biometric specifics (e.g. sensitivity, specifity). That would help to reduce the search for adequate filters.	Minor	To avoid duplucation of work the guidelinie refers to the InterTASC goup website. --> No changes to text
90	EFPIA	20	3.1.5.1	481-483	There should be more clarity/description here around what constitutes a "truncated" generic name since generally speaking, there are lots of sound-alike drug names. The citation refers to "truncated" names as tiotropium bromide being truncated to tiotropium - this is fine, however, the paper also reports that using a term like acetylsalicylic acid did not have high yield. Additionally, please advise on use of search terms with British spelling versus American spelling (should both be included, etc.)	Major	a) As stated in the guidelinie, it is sufficient to search with the truncated generic drug name (see Waffenschmidt 2015, PMID: 26099486). b) The generic drug name has the same British and American spelling. --> We added an example
91	EFPIA	20	3.1.5.1	481-483	For new drugs the generic name is not always sufficient. Adding the drug code and the trade name leads to more complete results.	Minor	This is not shown by Waffenschmidt 2015 (PMID: 26099486). --> No changes to text

92	EFPIA	21	3.1.5.2.	490 - 504	As previously stated. This should take into consideration what are the access rights to the databases. Medline/PubMed and CENTRAL are public databases but not Embase. The investigators can have or not access to search platforms like Ovid. If the investigators had contracted with Elservier for Embase access, the investigators can decide to use Embase search engine as the platform allowing to explore PubMed or Embase. When access to Embase is possible, we recommend to develop search strategies specific to Embase, but also to PubMed and consult the databases separately: PubMed in one side and Embase in the other side. When using Embase as search engine for exploring PubMed, we noticed some differences when compared to results issued from direct consultations using PubMed as engine search in MedLine.	Major	Please see comment 13 and 30. No further explanation are needed.
93	EFPIA	21	3.1.5.2.	500	and the “explode function	Linguistic	Text in the guideline adapted
94	EFPIA	21	3.1.7	525-526	"It should be ensured that each strategy fulfils the current quality assurance requirements." Again, this is an example for unnecessary content. This is trivial and self-evident.	Minor	We deleted the sentence
95	EFPIA	22	3.1.7	531-533	Automatic removal of duplicates is highly error-prone	Minor	Text in the guideline adapted
96	EFPIA	22	3.1.8.	548 - 550	The exclusion reasons should benefit from specific analysis. One study can have several reasons for exclusion (e.g. age, population definition, therapeutic scheme etc..). In this case rules can help when applying reason for exclusion.	Major	The guideline describes the technical process of citation screening. --> No changes to text
97	EFPIA	22	3.1.8	548-550	It should be clarified what is meant by 'decision': does the documentation about decision includes only "included" or "excluded" or also the reason for exclusion? Are there differences in the documentation for exclusion after title-/abstract-screening and after full-text screening?	Major	Section 3.5 refers to the fact that the documentation of the study selection is PRISMA-compliant. --> No changes to text
98	EFPIA	22	3.1.8	556	Making provision for a third reviewer to serve as 'tie breaker' should be recommended in situations where assessments between the 2 reviewers' assessments differ.	Minor	In this paragraph we describe the advantages of internet-based systems for study selection. Independent of this, creators of SR can of course involve a 3rd person. --> No changes to text
99	EFPIA	22	3.1.8.	560-562	Screening of titles and abstracts should be performed by two reviewers in a SLR. The word “usually” downgrades this aspect and should be replaces by “must involve” or “should involve” There should be a clear statement on the recommendation(s) on how to solve inconsistencies between the 2 reviewers	Major	a) Please see comment 98. Please also check Annexe 4 for concrete EUnetHTA requirements. b) The guideline describes the technical process of citation screening. --> No changes to text
100	EFPIA	22	3.1.8	561-2	it should be stated how the process proceeds if the two reviewers do not find a consensus	Minor	The guideline describes the technical process of citation screening. --> No changes to text
101	EFPIA	23	3.1.9	578	It should be included that documentation of reason for exclusion occurs not for hits excluded due to title / abstract screening.	Major	please see comment nr 97
102	EFPIA	23	3.1.10	593-601	A source update not more than 3 months prior to publication (as required by German HTA authorities for value dossiers) seems feasible	Minor	The guideline does not rule out short-term updates. --> No changes to text
103	EFPIA	23	3.1.10	599-600	The update search should be done before the assessment starts, not before the publication of the assessment.	Minor	In literature, the period until publication is usually considered. --> No changes to text
104	EFPIA	23	3.1.10	611 - 612	During updates, an overlap of 2 months is needed when performing the search compared to the previous one (e.g. initial search performed in July 2015, the update should consider a time frame from May 2015). The reason is that databases are being retroactively updated and new added papers the at the time of the initial search could be miss.	Major	If an interface allows the restriction to the entry date, then an overlapping of the search periods is not necessary. See explanations in the guideline (lines 611-614). --> No changes to text
105	EFPIA	24	3,2	621	Objectives of this section are not clearly depicted. We understood registers are being consulted for ensuring completeness when conducting a SR.	Major	Section 3.2.1 is a general introduction to study registers. --> No changes to text
106	EFPIA	24	3,2	621	The heading is confusing, “Clinical Trials Repositories” may be more appropriate as this section is about Clinical.Trials.gov; EU Clinical Trials Registers; ICTRP; ...		"Clinical Trials Repositories" is not a common term. --> No changes to text
107	EFPIA	24	3.2	621	Study registries have to be cosidered very specific. Registries like clinicaltrials.gov deliver sound information on the trial. Most others perform badly due to to the varying quality of the individual registry entries. In addition no trial results can be taken from there.	Minor	The requirements which study registers should be included can be found in chapter 3.2.3 well as in annexe 4 --> No changes to text
108	EFPIA	25	3.2.2	665	It should be defined what is meant with "too many hits".	Linguistic	Sentence deleted
109	EFPIA	25	3.2.3	672; 678-679	As EUnetHTA is an European process, a search in the European trial registry should be mandatory and not optional.	Minor	A search in EU Clinical Trials Register (EU-CTR) is mandatory for drug assessments, but not for others (e.g. medical devices). --> No changes to text
110	EFPIA	26	3.2.4.1	695-697	Synonyms are not always working. Especially for unauthorized drugs the drug code is essential to ensure complete results.	Minor	This statement refers to a current study (see Knelangen 2018; PMID: 29132833). --> No changes to text
111	EFPIA	26	3.2.4.2	714-715	"The York Health Economics Consortium provides a comprehensive overview of the search functions of different registries". This is the kind of information which should be expanded in the guidance as it delivers hands-on knowledge. Include this into the guidance (appendix) instead of only mentioning.	Major	It is not the aim of this guideline to reprocess knowledge prepared elsewhere. The link in the reference list (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home) simply takes you to the corresponding place on the Internet. --> No changes to text
112	EFPIA	27	3.2.6	740-741	"If no export function is available, the search results can be copied and pasted into Excel and processed." In contrast to the comment above this again is dispensable information.	Linguistic	We have deleted the sentence because the large study registers now offer a standardized export function.
113	EFPIA	27	3.2.8	755-757	What is the advice on reporting the search strategy/strategies of searching registries - since many of these have limited search functions and only simple syntax can be used, is it necessary to report the search strategy as one would with database searches?	Major	The documentation of search strategies is necessary and this is also required in the PRISMA-S reporting standard (see chapter 3.5.). --> no changes to text
114	EFPIA	28	3,3	772	Since October 2016, CSRs on all drugs submitted for approval have been made available on the EMA – Clinical data website.	Minor	Information on EMA - Clinical data can be found in chapter 3.4.1
115	EFPIA	29	3,3	779-810	Extending the concept of unpublished company reports beyond clinical study reports, there are likely to be other documents that the company may wish to supply to the reviewer, that would in-and-of-themselves, not be published directly (although they are likely to be published in article form). We agree that there should be protections against selective provision of these reports, and no specific conditions placed on their use, however, there are circumstances where the reports may contain information considered acadamic or commercially confidential, and mechanisms should be in place to respect that confidentiality. Furthermore, where reports themselves are not in the public domain (most CSRs should be so for newly authorised medicines) there should be some consideration/guidance to authors in how they select information for reporting. The concept of freedom to report relevant data, relies on the concept of data relevance. Where this is debatable, and where data is not reported (as not considered relevant), but might provide specific context for data that is considered relevant and reported by the authors, then some remedy will be required in cases where the public cannot access the totality of the source material directly in the public domain. It is unreasonable to faciliate potentially biased reporting of unpublished data becuase one group considers it relevant or not - such decisions for selective reporting should be justified and subject to some arbitration process with this is in dispute.		a) From the point of view of EUnetHTA*, study methods and study results are not “commercial in confidence” information. Furthermore, manufacturing or other trade secrets are not required for HTA reports. (Adopted from the commentary on the Guidelines Version 1.0.) b) The consideration/guidance to authors in how they select information for reporting is not part of this guidelinie *“EUnetHTA strongly supports the statement that clinical trial data (indeed for all trials, involving medicines, devices or other healthcare interventions) cannot be considered commercially confidential information (CCI), and that the interests of public health outweigh consideration of CCI for clinical trial data.” http://www.ema.europa.eu/docs/en_GB/document_library/Overview_of_comments/2014/09/WC500174222.pdf --> No changes to text
116	EFPIA	28	3.3	794-798	It is unclear if the CSRs should only be included in the search for systematic reviews or also in the search for HTA assessments. Inclusion of CSRs (from competitors) in the search process is problematic, as it is uncertain, whether these documents (which are available on the EMA website, for example) may be legally used for this purpose. According to the terms of use published by EMA, “the User may use the Clinical Reports for general information and other non-commercial purposes, including non-commercial research purposes, subject to these Terms” and “The User is not granted any intellectual property or other commercial rights in relation to the Clinical Reports other than as expressly set out in these Terms.”	Major	CSR can be used for HTA assessment according to the terms of use (please check the EMA document in which there are explanations of the terms of use: https://www.ema.europa.eu/en/documents/report/questions-answers-european-medicines-agency-policy-publication-clinical-data-medicinal-products_en.pdf) --> No changes to text
117	EFPIA	28-29	3.3	795-809	Full information disclosure is generally acceptable but must not compromise publishability of results in peer-reviewed journals that contribute to the necessary scientific discourse. Also, disclosure of annexes and narratives would compromise confidentiality of patient data and would possibly be outright illegal. In general, national HTA authorities should not request additional data beyond the exhaustive body of evidence already submitted to the regulatory bodies (EMA).	Major	It is important to note that the CSRs are not published, but the study results and methodology. Since HTA has other research questions than the EMA, other data (other analyses) may also be required. --> No changes to text

118	EFPIA	30-31	3.4.2	869-889	A requirement for queries to authors to be made for unpublished data seems is likely to be of limited value in most cases for SLRs provided by Companies and/or authors in the context of REA/JCA. Company requests might be seen as commercial and therefore denied - especially if the studies are sponsored by other companies - but primiarily the biggest limitation is the timeline within which such an SLR must be conducted, and its findings made available for comparative effectiveness analysis. This 'belt & braces' approach should therefore be qualified in the guidance as not essenstial, and absense of request for such data should not be seen as resulting in an incomplete SLR.		As stated in 3.4.2 and in Annexe 4, queries to authors are an optional source. --> no changes to text
119	EFPIA	31	3.4.3	891-911	Extensive indirect searching is helpful to confirm the core trials or studies have been identified, but in the context of searching for data on long-standing treatments that might be considered as comparators is likely to lead to large numbers of search hits, many of which will be of historical value only and not represent either the modern use of those medicines today, or will utilise study designs and endpoints that will not be compatible with indirect comparative effectiveness analysis. The extent to which this problem will arise is difficult to assess, but the guideline should recongise the value of indirect searching when it adds incremental value, rather than when it requires disproportionate effort and hinders use of the SLR findings in meta-analyses. The guideline might therefore indicate that when indirect seraching is unlikely to represent a useful additional strategy in the context of the decision problem and the time available for the researcher, justification of its exclusion or minimal application should be sufficient for the SLR to still be considered complete.		When using other search techniques, we only recommend checking reference lists by default. --> We've reformulated the section
120	EFPIA	31	3.4.4	917	"...mostly..." instead of "...often..."	Linguistic	No changes to text
121	EFPIA	31-32	3.4.4	913-937	The section on the use of conference reports seems sensible position in many respects, and especially so in relation to information being sought on mature products. However, perhaps the section should also reflect that new / pre-approval products may rely on such reports as the early public communication of results, and these materials may represent the information contained within study reports that can be cited directly; other key information in the study report being considered academic-in-confidence at the time of the search and review. The issue of important data made available in conference abstracts long before the full paper is published is not addressed is not discussed. In some instances, at a given date, this could impact the conclusions in a way that they are obsolete if the data from the abstract is not taken into account. Sometimes, conference posters give data that matches the PICOS of interest, and are of crucial importance for rapidly evolving medical fields. Some guidance on this relatively frequent issue will help to incorporate this type of information in the SLR while mitigating the risk of bias		The guideline does not exclude the use of abstracts in general. However, the guideline describes the reasons why the inclusion of abstracts is in most cases not meaningful. --> No changes to text
122	EFPIA	32	3.4.4	925-930	For the benefit assessment, only documents are to be used that meet the criteria of the CONSORT statement and contain primary data that is relevant for answering the question defined in the dossier (full publications, reports or registry entries). Therefore, a search for conference abstracts should not be performed.	Major	That's why we recommend this search only in exceptional cases. --> No changes to text
123	EFPIA	32	3.4.4	935-937	If a systematic review or meta-analysis includes both full text papers and abstracts, authors should make clear which publications are abstracts and which are full text. Also if possible, an assessment (e.g., sensitivity analyses) should be conducted to determine whether results differ based on inclusion of abstracts	Minor	The analysis of the data is not part of the guideline. --> No changes to text
124	EFPIA	32	3.4.4	935-937	It may be useful to also have some guidance around how one should deal with data reported in an abstract and subsequently not reported in the full text publication of the same study, or vice versa. Should these data/results be included or should the most recent publication be taken as the only source of findings from said study.	Minor	The analysis of the data is not part of the guideline. However, there is a general section on reporting bias in the guideline (Section 2.2.3). --> No changes to text
125	EFPIA	32	3.5	953-4	it should be clarified if this sentence is only relevant for searches in bibliographic databases or for searches in registries as well	Minor	PRISMA-S refers to bibliographic databases as well as other information sources (e.g. study registers). No changes to text
126	EFPIA	32	3.5	954-956	The list of included studies should be reviewed by an expert on the topic of interest. It is currently admitted papers can be added by expert in case the missed in set of evidence obtained from data sources consultation.	Major	Section 3.5 describes reporting in the report. --> No changes to text
127	EFPIA	33	4	961-966	Quality checks on all eligible primary studies should be recommended, not only for studies identified from published SRs. How these checks influence the final number of included studies should also be reported.	Minor	We agree that the primary studies must meet the inclusion criteria of the report. --> Text adapted.
128	EFPIA	33	4 (bullet 2)	978-979	An update is not only a matter of changing the time horizon. Sometimes an update on Interventions/comparators or outcomes is needed when the first step is using SLRs already available. An example is in oncology SLRs based on survival data when the researcher is interested in survival AND Progression Free Survival (PFS). The available SLR could be used for survival data but has to be updated for period not covered but also and the PFS. Similar situations are seen when SLR include only some of the comparators of interest but not all.		We have adapted the text to take account of this aspect (line 1022-1023).
129	KIHT	140-145			Comments: Activity No: 140-145 if possible, we are, suggesting that Truncations in PubMed should be increased to above 600 variations.		Unfortunately, we have no influence on the search functionalities of Pubmed. --> No changes to text
130	KSR	17	3.1.1	363	found in ~~the~~ Annexe 3	linguistic	Text proposal adopted
131	KSR	17	3.1.1	364	Change Press to PRESS	minor	Text proposal adopted
132	KSR	18	3.1.2	375	articles [4,55,56] which can subsequently be used in the development of the search strategy	linguistic	Text proposal adopted
133	KSR	18	3.1.2	378	preselected information sources [5,52,53,57] such as the Cochrane Database of Systematic Reviews, Epistemonikos, KSR Evidence	minor	KSR Evidence and HTA database added
134	KSR	18	3.1.2	379	and, if relevant, the websites of HTA agencies (e.g. NICE and AHRQ. In order to	linguistic	Text proposal adopted
135	KSR	19	3.1.3	413	Validated study filters should be used for search concepts on study design (see Section	linguistic	Text proposal adopted
136	KSR	19	3.1.4	423	This is because journal inclusion rates differ between databases [65,66]	linguistic	Text proposal adopted
137	KSR	19	3.1.4	426, 427	There is insufficient empirical evidence so far on how many and which databases should be regularly searched.	linguistic	Text proposal adopted
138	KSR	19	3.1.4	431-432	It is also recommended that an additional search for non-indexed information be undertaken e.g. in PubMed or MEDLINE (Ovid) to ensure that all references, especially the most recent, have been identified	minor, linguistic	Text proposal adopted
139	KSR	19	3.1.4	435	has been insufficiently investigated, and many such databases provide	linguistic	Text proposal adopted
140	KSR	19	3.1.4	436	restricted functionalities [75,76]. However, for some objectives the use of subject-	linguistic	Text proposal adopted
141	KSR	20	3.1.5.1	456-457	searches [86,92] are systematically analysed for word frequency by a text-analytic software package. These software packages vary in cost and functionality. A list of text-analytic tools can	minor, linguistic	Text proposal adopted
142	KSR	20	3.1.5.1	459	In the next step, identified terms are assigned to the individual concepts of the search	linguistic	Text proposal adopted
143	KSR	20	3.1.5.1	460-461	Delete "independently of which approach was chosen to identify subject headings and free-text terms."	linguistic	From our point of view, it is important to mention that from this step on, the objective and conceptual approach will continue identically. --> No change made to the guideline
144	KSR	20	3.1.5.1	467	Terms for topics or study designs need not be identified if validated, high-quality filters	linguistic	Text proposal adopted
145	KSR	20	3.1.51.1	471	If the search is restricted to RCTs, validated and highly sensitive study filters, which ~~should~~	linguistic	Text proposal adopted
146	KSR	21	3.1.5.2	492	determined, the actual strategy can be developed. ~~Ideally,~~ Each database should be searched separately. Cross-database searching is only acceptable if the search strategy is applicable to each database. For example, free-text terms can usually be applied across databases.	minor, linguistic	Text proposal adopted
147	KSR	21	3.1.6	519	[12], i.e. it tests whether relevant references identified beforehand (see Section 3.1.2)	linguistic	Text proposal adopted
148	KSR	22	3.1.8	551	The selection of references is usually administed in the RMS or by manual handling of	linguistic	Text proposal adopted
149	KSR	22	3.1.8	562	performed by at least two reviewers [121]. Current automatio approaches ~~mainly~~ aim to	linguistic	Text proposal adopted
150	KSR	22	3.1.8	564-565	process [123]. The RCT classifier, RobotSearch [124] is an appropriate tool for limiting screening results through prioritization [125] and has been	linguistic	Text proposal adopted
151	KSR	23	3.1.10	599	possible. Ideally, the last search in an EUnetHTA assessment should therefore be	linguistic	Text proposal adopted
152	KSR	25	3.2.1	650-651	However, entries may be incomplete, contain 650 errors [155] or be changed after registration	linguistic	Text proposal adopted
153	KSR	25	3.2.1	657	Previously systematic reviews may not routinely searched study registries [46,167]	linguistic	Text proposal adopted
154	KSR	25	3.2.2	662-664	It is advisable to search using the most specific concept terms first, as this will probably generate the lowest number of hits.	linguistic	Text proposal adopted
155	KSR	25	3.2.3	671	Several registries should be searched, as no single registry contains all studies	linguistic	Text proposal adopted
156	KSR	25	3.2.3	672	As a minimum, the ICTRP Search Portal and ClinicalTrials.gov should be searched.	linguistic	Text proposal adopted
157	KSR	25	3.2.3	676-677	For this reason, ClinicalTrials.gov should always be searched directly	linguistic	Text proposal adopted
158	KSR	25	3.2.3	678-679	For SRs of drugs, the relevant company registry and EU-CTR should be searched.	linguistic	Text proposal adopted
159	KSR	25	3.2.3	681-682	are often no longer updated when funding ceases	linguistic	Text proposal adopted
160	KSR	26	3.2.3	682-683	Consequently, they are not very useful and should only be searched for in exceptional cases	linguistic	Text proposal adopted
161	KSR	26	3.2.4.1	688-689	The trial registry search should use terms from the strategy used for the bibliographic database searching	linguistic	Text proposal adopted
162	KSR	26	3.2.4.1	693-694	This is helpful because study registries only provide 693 limited search functions	linguistic	Text proposal adopted
163	KSR	26	3.2.4.1	696	in ClinicalTrials.gov (after 2005).	linguistic	The year refers to newly approved drugs. No change made.
164	KSR	26	3.2.4.1	697	In ICTRP and EU-696 CTR, the drug code should also be included	linguistic	Text proposal adopted
165	KSR	26	3.2.4.1	697-698	In Clinicaltrials.gov, simple search terms are usually sufficient when searching for the therapeutic indication, as the "search for synonyms" function performs well in this registry.	linguistic	Text proposal adopted
166	KSR	26	3.2.4.1	699-700	In the ICTRP Search portal and EU-CTR [145], a more comprehensive approach is recommended.	linguistic	Text proposal adopted
167	KSR	26	3.2.4.2	716-717	If appropriate, a sensitive search should be conducted as a single concept search using the "basic search" function	linguistic	Text proposal adopted
168	KSR	27	3.2.5.	721-722	The peer review of study registry search strategies should follow the approach followed for bibliographic databases.	linguistic	Text proposal adopted
169	KSR	27	3.2.5.	727-728	A set of relevant registry entries can be compiled, by using relevant studies picked up in the bibliographic database searches (see Section 3.1.2)	linguistic	Text proposal adopted
170	KSR	27	3.2.5.	729-730	Although it is not always possible to link all the relevant studies to corresponding registry entries, as not all journal articles include study identifiers such as National Clinical Trial numbers	linguistic	Text proposal adopted
171	KSR	27	3.2.5.	738-739	which can ~~then~~ be imported into a RMS using an import filter [30]. The 738 search results can ~~then~~ be processed for screening.	linguistic	Text proposal adopted
172	KSR	27	3.2.7	748-749	the registry entries should be independently screened by two reviewers.	linguistic	Text proposal adopted

173	KSR	28	3,3	799-800	For example, IQWiG currently applies the following approach for this purpose [190]: before 799 requesting data,	linguistic	Text proposal adopted
174	KSR	28	3,3	781	Although CSRs are considerably longer than journals publications	linguistic	Text proposal adopted
175	KSR	28	3,3	787	Since 2013, GlaxoSmithKline (GSK) has published CSRs of all GSK	linguistic	Text proposal adopted
176	KSR	28	3,3	802	~~In this context,~~ To avoid bias by	linguistic	Text proposal adopted
177	KSR	28	3,3	804	procedure then follows: firstly,	linguistic	Text proposal adopted
178	KSR	29	3.4.1	833-834	Until recently, regulatory agencies did not publish complete CSRs but made available related documents from the approval process	linguistic	Text proposal adopted
179	St. Vincent's University Hospital	0 general			Mixed methods reviews include qualitative studies as well as quantitative. These are imporant as they frequently focus on person- or patient-centred values (Patient and Public Involvement, PPI). A section on carrying out mixed-methods reviews would help ensure qualitative data is integrated especially for HTAs.	major	Mixed methods methodology is not widely used in the international HTA context. Therefore, the approach is not taken into account in the guideline. --> No changes to text
180	St. Vincent's University Hospital	18	3.1.2	379-381	To avoid duplication and waste, check in Prospero and Cochrane Library to see if your proposed project is already and recently being addressed. If so then check with authors to see whether their project is still live or whether they have changed focus in any way. You may then decide to redefine your question or a collaboration may be possible.	minor	Text proposal adopted
181	St. Vincent's University Hospital	15	2.2.1	301-303	http://www.equator-network.org/reporting-guidelines/prisma-protocols/	minor	Text proposal adopted
182	St. Vincent's University Hospital	21	3.1.7	524-525	A search narrative should be included to clarify any non-standard decisions or anomalies in the search strategy.	minor	The guideline refers in chapter 3.5 to PRISMA-S. There the narrative description of search strategies is mentioned. --> no changes to text
183	St. Vincent's University Hospital	0 general			Include definitions (where available) and clarification of different types of reviews - rapid, living, etc - and when and why it would be appropriate to use them. Be aware of any limits that have been applied especially to rapid reviews.	minor	This comment goes beyond the horizon of this guideline. No change made to the guideline
184	NHS HEALTHCARE IMPROVEMENT SCOTLAND	11		211	4th recommendation: maybe include mention of platform or interface for clarity? This is clearer in the annexe	"linguistic"	Text proposal adopted
185	NHS HEALTHCARE IMPROVEMENT SCOTLAND	11		211	5th recommendation: maybe include something about any validated search strategies or filters should be acknowledged and cited for clarity? This is clearer in the annexe	"linguistic"	This is an aspect that has been added under 4th recommendation.
186	Pharmerit International	20	3.1.5.1	475-477	The omission of a study design filter in a search strategy for a systematic review is often not a feasible approach with vasts amount of literature. For instances where the use of non-randomised data are needed what specific guidance is there to identify this in a systematic way while maintaining a feasible number of references for review?	Major	At the moment there is no validated filter available to limit a search Currently, there is no validated study filter to search for non-randomized studies. --> No changes to text
187	Pharmerit International	24	3.2.1	641	Suggest addition of "on": "Study registries are publically available and commonly **on** web-based databases or platforms"	Liguistic	Suggested text adopted.
188	Pharmerit International	25	3.2.1	649-652	The point around study registries having incomplete or incorrect data, and that data can change throughout the lifetime of the study record is a concerning one for systematic reviews. It would appear that these are not realiable sources of data and some clear guidance on what (if anything) should be extracted from these records is needed. Should these registries be used purely to identify ongoing studies that are likely to publish in the near future? Or is it expected that results from these records are extracted and included in the systematic review?	Major	The search in study registers is intended for both ongoing and completed studies and completed studies with results. How the data are handled is not part of the guideline. However, inconsistencies may also occur between several articles of a study as well, which have to be assessed by the authors. --> 3.2.1 We have added that the search should include ongoing and completed studies as well as completed studies with results.
189	Pharmerit International	33	4	962-964	Request for additional guidance: When is a systematic review considered "up-to-date, high-quality and relevant SR" and acceptable to be used for a layered approach?	Major	This information can be found in Chapter 4 later in the text. Please see line 972-975 --> no changes to text
190	Pharmerit International	33	4	962-964	Request for additional guidance: Are there certain fields of evidence (e.g. RCT, observational studies, utilities, cost-effectiveness, resource use/cost inputs) that are more suitable for the layered approach?	Major	Whether or not this approach is chosen depends rather on whether there are high-quality SRs on the respective topic. --> no changes to text
191	Pharmerit International	33	4	962-964	Request for additional guidance: Are there situations when a layered approach is more or less justifiable?	Major	please see comment nr. 190
192	Pharmerit International	33	4	963	Request for additonal guidance: Which source can best consulted for practical instructions on how to best perform review with layered approach? The refereces by Tricco et al. (broad methodology of rapid reviews) and Robinson et al (existing correspondence on the layered approach) do not provide this information.	Major	This approach is often used in practice without the procedure being described in detail.An example of the practical implementation can be found here: EUnetHTA report on osteoporosis (https://www.eunethta.eu/wp-content/uploads/2019/09/2019-09-13_OTCA19_Screening-for-osteoporosis_final.pdf) --> No changes to text
193	Pharmerit International	31	3.4.4	913-924	"... it is not recommended to routinely search for abstracts and reviewers should always try to obtain the full report or further study details, before considering whether to include the results in the review [5,224]." Suggestion/recommendation: (routinely) search for conference abstracts for the 1-2 most recent years, because updates of trials might have been published as abstracts and are not yet available as full report.	Minor	In the guideline we have given the reasons why we do not recommend this procedure as standard. --> No changes to text
194	AIFA	24	3.2	647	We suggest to add in the second row of the table 1 (Regulatory registry) the following study registry: "TrialCheck" and the following reference in the Bibliography: U.S. Government Department of Health and Human Services. TrialCheck [internet]. [cited 13.09.2019]. Available from: https://www.eviticlinicaltrials.com/services/"	major	The data set from TrialCheck comes from ClinicalTrials.gov. It is therefore not a separate study registry. --> No changes to text
195	AIFA	25	3.2	647	We suggest to add in the last row of the table 1 (Meta-registry) the following study registry: "ISRCTN registry (International Standard Randomised Controlled Trial Number)" and the following reference in the Bibliography: "BioMed Central Ltd. ISRCTN registry [internet]. [cited 13.09.2019]. Available from: http://www.isrctn.com/"	major	The ISRCTN Study Register is also searched via a search in the ICTRP Search Portal. --> No changes to text