INSTRUCTIONS FOR AACPDM CARE PATHWAY DEVELOPMENT 2020 EDITION

Prepared by
the Care Pathways Methodology Sub-committee:
Kat Kolaski, Author
Other Contributors:
Mohan Belthur, Angela Boisselle
Stephanie DeLuca, Lynne Romeiser Logan
Stacey Miller, Leanne Sakzewski, Seth Warschausky

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PART 1. GENERAL INSTRUCTIONS

1. Definition of an AACPDM Care Pathway:

Care Pathways are guidelines for the health care of individuals with childhood-onset disabilities. Their main goal is to develop recommendations that allow users to understand the evidence on a topic and apply it to clinical practice. Practice recommendations provided by Care Pathways are based on the best available evidence from systematic reviews developed with rigorous methodologic standards. They are graded for their probable accuracy (i.e., quality) and the confidence with which they can be used (i.e. strength) for the purpose of making clinical decisions. The systematic processes used in the decisions and judgments involved during Care Pathways development are transparent and explicitly described.

2. Priority Setting for Care Pathway Development

Care Pathways are developed to address one of the following: health conditions (e.g., dystonia), interventions (e.g., hip surveillance), and diagnostics (e.g., early identification of cerebral palsy). Priority setting for topics is directed by the Care Pathways Committee who consider input from key stakeholders and consumers. This ensures resources for Care Pathways are devoted to those areas where recommendations from the AACPDM will provide the greatest benefit. Surveys and polls will be distributed to attendees of the AACPDM's annual meetings in order to elicit suggestions for Care Pathways topics and for ranking of potential topic importance. The Care Pathways webpage, which is accessible to the general public as well as AACPDM's general membership, will provide a link for Care Pathway topic suggestions and post a list of these suggestions.

Applications for Care Pathway development on suggested topics--or other topics of interest to individual AACPDM members-- can be submitted to the Committee. Review of Care Pathways applications involves consideration of the following:
-Importance and relevance of the topic
-Prevalence of the disease or condition
-Amount of practice variation or controversy on the topic
-Cost and resource implications of the interventions addressed by topic
-Potential to improve patient care and outcomes
-Availability of an existing body of evidence related to the topic; in some cases, a scoping review may be needed to evaluate the availability of high-quality evidence on which recommendations will be based.

3. Foundational principles for Care Pathways

3.1 General Methodology

Sound methodology should be used for all aspects of Care Pathways. Assuming most Care Pathways developers are not methodologic experts, the tools and procedures to be used for Care Pathway development are limited in number and not chosen by Care Pathways developers. This is done in order to ensure the validity and credibility of the clinical recommendations produced. Characteristics of the recommended tools and procedures used to develop, update, and revise AACPDM Care Pathways include the following:

1. Developed by methodologically sophisticated/knowledgeable groups working in concert worldwide across disciplines/medical societies/organizations;
2. Tested over time;
3. Endorsed by notable organizations;
4. Provide support for users;
5. Have the ability to maintain high quality standards by monitoring new developments in evidence-based medicine in general as well as ongoing evaluation and continual updating of their specific tools/procedures.

3.2 Specific Methodology

AACPDM Care Pathways endorses the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology for developing evidence-based clinical recommendations. GRADE was developed by an international panel, including members of some of the premier evidence-based practice centers. GRADE is a well-developed formal process to assess the quality of scientific evidence in systematic reviews and to develop recommendations for clinical practice that are as evidence-based as possible. GRADE has been adopted by many global medical institutions and associations, including the WHO and Cochrane Collaboration. It is currently considered the gold standard method for producing clinical recommendations.

GRADE specifies an approach to framing questions, choosing and prioritizing outcomes of interest, evaluating the evidence, including making explicit the risk of various biases, and considering issues of imprecision, inconsistency between studies, and indirectness (i.e., making inferences using evidence from a similar population). In arriving at one of four types of possible recommendations, GRADE incorporates evidence about costs, benefits and harms, and explicitly considers the values and preferences of patients and society at large. GRADE also provides clinicians, patients, and policy makers with a guide to using those recommendations.

THE GRADE evidence- to-decision framework is complex, but many resources are available to assist developers of AACDPM Care Pathways including:

(1) A series of papers, the majority of which are published in the *Journal of Clinical Epidemiology,* contain detailed background information and instructions for every step of GRADE (See Appendix I, pages 15-17, for complete reference list).

(2) GRADE Handbook: https://gdt.gradepro.org/app/handbook/handbook.html

(3) GRADEpro GDT software: https://gradepro.org/

(4) The GRADE Working group website has links to a variety of instructional materials, including tutorials and presentations and annual comprehensive courses on GRADE: http://www.gradeworkinggroup.org/.

3.3 Terminology

To reduce ambiguity and confusion, all Care Pathways development tools (including these instructions) and their end products should be written in in plain and explicit language with consistent use of evidence-base medicine terminology. For reference, see the following resources:

https://ebm-tools.knowledgetranslation.net/resource/glossary (From the Knowledge Translation Program, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON)

https://cebgrade.mcmaster.ca/checklistglossaryprintable.pdf (From the Grade Centre at McMaster University, this is a glossary of terms and acronyms appearing throughout the GDC checklist.)

https://www.cebm.net/2014/06/glossary/ (From Center for Evidence Based Medicine, University of Oxford)

https://bestpractice.bmj.com/info/toolkit/ebm-toolbox/a-glossary-of-ebm-terms/ (From British Medical Journal Best Practice)

https://gdt.gradepro.org/app/handbook/handbook.html GRADE Handbook GRADE guidance with extensive discussion of each topic.

3.4 Recommended Procedures and Tools

3.4.1 Guidelines International Network (GIN) - McMaster Guideline Development Checklist (GDC):
Available at: https://heigrade.mcmaster.ca/guideline-development/using-checklist
Published in 2014, the GDC comprehensively operationalizes the GRADE evidence-to-decision framework. It is organized into 146 steps across 18 topics addressing all stages of the guideline enterprise from planning and development to implementation and evaluation. Users of the checklist should become familiar with the topics and steps before applying them. The online version of the checklist includes links to learning tools, articles and guides to learn about the items in the checklist, as well as links to resources and tools for implementing the items.

3.4.2. GDC-Care Pathway Checklist
Many of the steps outlined in the GDC warrant explanation, clarification, or provision of specific directions for AACPDM Care Pathway developers. To do so, a merged form of the GDC was created for Care Pathways (GDC-Care Pathway). The GDC-Care Pathway Checklist (hereafter referred to as "GDC-CP") contains all of the original GDC content, but adds additional columns for Care Pathways developers. One column contains specific guidance on Pathway development steps and another references the ten phases of the Care Pathways development process outlined in this document (see pages 10-15). The other columns can be used by Care Pathways developers for notes and documentation.

Care Pathways developers should follow the original GDC steps for general guidance, but review the Care Pathways specific instructions found alongside them. They are also encouraged to use all GDC

and other resources available online and listed above. A certain degree of redundancy between this Instruction document and the GDC-CP should be anticipated; this was done to ensure comprehensiveness. Consultation with the Care Pathways Committee should be sought when assistance is needed regarding any GDC-CP Checklist topic or specific step.

Preparatory activities for Care Pathway development addressed in Topics 1-9 of the GDC-CP are incorporated into the application process for potential Care Pathway Development. After final approval for Care Pathway development is obtained, the GDC-CP can be used as the protocol for further Care Pathway development. It allows Care Pathway developers to plan and track their progress and to ensure no key steps are missed. Following the steps of the GDC-CP increases the likelihood of a Care Pathway meeting requirements for clinical guidelines as specified by the Institute of Medicine, and for receiving a favorable evaluation using credibility assessment tools such as AGREE II.

3.4.3. AGREE II (Appraisal of guidelines for research and evaluation)

Available at: https://www.agreetrust.org/resource-centre/agree-ii/

AGREE II was developed to address the issue of variability in the quality of practice guidelines. It can help guideline developers and users assess the methodological quality of guidelines.

3.4.4. ***AMSTAR 2 (MeaSurement Tool to Assess Systematic Reviews)***

Available at: *https://amstar.ca/Amstar_Checklist.php*

AMSTAR (2007) was developed to address the variation in quality and empirical validation of systematic reviews of randomized controlled trials. AMSTAR 2 (2017) is an updated version of AMSTAR which enables appraisal of systematic reviews of both randomized and non-randomized studies of healthcare interventions.

3.4.5 ROBIS (Tool to assess risk of bias in systematic reviews)

Available at: *www.robis-tool.info*

ROBIS assesses both the risk of bias in a systematic review and the relevance of a review to the question(s) being researched for development of a guideline. It can be used to evaluate intervention, etiology, diagnostic, and prognostic reviews.

3.4.6 PRIOR (Preferred Reporting Items for Overviews of Reviews)

Overviews of reviews (sometimes referred to as “overviews of systematic reviews,” “reviews of reviews,” “reviews of systematic reviews,” or “umbrella reviews”) analyze the results of multiple related systematic reviews. PRIOR is a reporting guideline for overviews of reviews of healthcare interventions that is currently in development. For guidance until the final tool is available, please refer to:

Lunny C, Brennan SE, McDonald S, McKenzie JE. Toward a comprehensive evidence map of overview of systematic review methods: paper 1 –purpose, eligibility, search and data extraction. Syst Rev. 2017;6(1):231.

Lunny C, Brennan SE, McDonald S, McKenzie JE. Toward a comprehensive evidence map of overview of systematic review methods: paper 2 — risk of bias assessment; synthesis, presentation and summary of the findings; and assessment of the certainty of the evidence. Syst Rev. 2018;7(1):159

3.4.7. 2015 PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis)

Available at: *http://annals.org/aim/fullarticle/744698/prisma-statement-reporting-systematic-reviews-meta-analyses-studies-evaluate-health*

The original PRISMA checklist was developed in 2009 to ensure all the critical methodologic components of a systematic review are reported. There are currently over 400 PRISMA guidelines housed on the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network's Website. PRISMA extensions relevant to Care Pathways include:

- 2013 PRISMA-Abstracts for journal and conference abstracts
- 2016 PRISMA-harms for reporting harms in systematic reviews
- 2018 PRISMA-ScR Checklist for reporting scoping reviews
- PRISMA-C Checklist for reporting systematic reviews for children, In progress
- PRISMA-PC Protocol for systematic reviews for children, in progress

3.4.8. Risk of bias assessment tools for primary research studies

These will be used by Pathway Teams who undertake a new systematic review(s) to inform a new or revised Care Pathway (See PHASE V for details). Two specific tools are recommended by GRADE: Cochrane Risk of Bias Tool for randomized controlled trials, and ROBINS-1 for all types of non-randomized studies of interventions (NRSI). See Cochrane Handbook for additional information and links to tools. Justification for the use of other tools to appraise these study designs in a new or updated systematic review(s) must be submitted for approval by the Care Pathways Methodology Sub-committee. Additional tools will be needed to evaluate risk of bias in primary research studies that are not RCTs or NRSI. Suggestions for risk of bias assessment tools for these include:
-*RoBiNT for evaluation of single-subject design research*. Reference: Tate *et. al*. Neuropsychological Rehabilitation, 2013; 23: 619–638, http://dx.doi.org/10.1080/09602011.2013.824383 DOI: 10.1111/j.1469-8749.2007.02005.x

-Johanna Briggs Institute (JBI) Checklists for Analytical Cross Sectional Studies, Diagnostic Test Accuracy Studies, Economic Evaluations, Prevalence Studies, Qualitative Research

https://urldefense.proofpoint.com/v2/url?u=https-3A__joannabriggs.org_ebp_critical-5Fappraisal-5Ftools&d=DwIFAg&c=yzGiX0CSJAqkDTmENO9LmP6KfPQitNABR9M66gsTb5w&r=KUNAV1nA0lCR_1Hze-At2zmbo98saAAmV848HmLmIIE&m=8Lee-YBAnlb-1fb8dNt67cAfMqrnobSXjobTXw6Rm18&s=Hfizf9ARIdm_ilwmx1oaO8nLwwoT0s1VUwU7eht9iTM&e=

-Critical Appraisal Skills Programme (CASP) Checklist for qualitative research

https://urldefense.proofpoint.com/v2/url?u=https-3A__casp-2Duk.net_wp-2Dcontent_uploads_2018_01_CASP-2DQualitative-2DChecklist-2D2018.pdf&d=DwIFAg&c=yzGiX0CSJAqkDTmENO9LmP6KfPQitNABR9M66gsTb5w&r=KUNAV1nA0lCR_1Hze-At2zmbo98saAAmV848HmLmIIE&m=8Lee-YBAnlb-1fb8dNt67cAfMqrnobSXjobTXw6Rm18&s=iJQK3Z5-PnjkgeI2YrTww6hjHF3vQEU05Ttdj5uD8zY&e=

-Mixed Method Appraisal Tool (MMAT) Version 2018

http://mixedmethodsappraisaltoolpublic.pbworks.com/

3.4.9 Non-intervention Systematic Reviews

Although intervention effectiveness will likely be the main focus of AACPDM Care Pathways, they may also require evidence from research about diagnosis and prognosis. Systematic reviews of these study types can be complex and challenging, and require specific methodologies.

3.4.9a Systematic Reviews of Diagnostic Test Accuracy (DTA)

Systematic reviews of diagnostic test accuracy are used to provide a summary of test performance based on all available evidence, evaluate the quality of published studies, and account for variation in findings between the studies. There are different procedures and tools recommended for this type of review, including risk of bias assessments specifically for primary studies reporting DTA evidence. Cochrane offers extensive resources for this type of review, including a Handbook, software for meta-analysis, and various trainings. For more information, consult the Cochrane Screening and Diagnostic Test Accuracy Groups's website at: https://methods.cochrane.org/sdt/. The Johanna Briggs Institute also provides a Reviewer's Manual and offers several practical tools for development of this type of review

3.4.9b Systematic Review of Prognosis Studies

According to Cochrane, there are several types of reviews in this category: 1) Overall prognosis reviews give insight into occurrence of certain outcomes in a certain time frame, for a group of individuals with a certain health condition (not necessarily a disease); 2) Reviews on prognostic factors identify variables that are prognostic for a certain outcome in a certain individual within a given timeframe; 3) Prognostic model reviews combine prognostic factors in a single model to make personalized predictions for individuals with a certain health condition; and 4) Reviews investigating predictors of treatment effect aim to identify individuals' factors that are associated with the effectiveness of a certain treatment

These reviews are very different from intervention and diagnostic test accuracy reviews, both methodologically and regarding the clinical question asked. For guidance, consult the the Cochrane Prognosis Methods Group's recommendations available at:
https://methods.cochrane.org/prognosis/

4. Care Pathways Development Team Structure

The development of a Care Pathway involves many different groups and responsibilities.

4.1 Care Pathways Committee

This AACPDM committee establishes overall policies and procedures, suggests topics and approves applications for Care Pathways development, manages Conflict of Interest (COI) issues when not resolved within the Team, monitors existing Care Pathways, and provides oversight to Pathways in development or undergoing a 5 year review.

Provision of oversight is facilitated by assignment of a Liaison to each Care Pathway Development Team. It is suggested that the Liaison serve as an active, contributing member in the Evidence Group and/or Panel (provided there is no COI). The Liaison should be included in all Care Pathways Development Team meetings, teleconferences, and electronic communications.

At various intervals during Pathway development, the Committee reviews essential documents and reporting information including:
1) Completed GDC-CP Checklists, proposed timelines, and Team Roster
2) COI disclosures of all Care Pathway Development or Revision Team members
3) Protocols of new or updated systematic reviews submitted for registration
4) Systematic reviews completed by Care Pathways Teams *prior* to initiation of evidence-to-recommendation steps and submission for publication.
5) Final Care Pathway presentation items and copies of all reporting items *prior* to posting online

Care Pathway Teams should inform their Liaison of concerns that arise during the initial development of the Pathway or its subsequent review. Such concerns include--but are not limited to--COI issues, appeal for changes to Care Pathway methodology (e.g., use of alternative appraisal tools, exemptions and/or modifications of required GDC-CP steps due to specific circumstances), and timeline extensions. These concerns will then be discussed by the Committee, and their responses and/or directives communicated back to the Teams by the Liaison.

4.2 Care Pathway Development Team

Participants should include individuals with the scientific and/or clinical expertise germane to the Care Pathway topic as well as a range of clinicians with diverse representation from different geographical regions, genders, ethnicities, and practice settings (i.e., academic vs non-academic). All participants serve as volunteers. They should be AACPDM members in good standing. Exceptions for participants who are non-AACPDM members are considered when representatives of clinical diversity or necessary experts are not available from within the AACPDM membership.

Responsibilities of the various participants on the Care Pathway Development Team must be clearly established with assignment to a specific sub-group or groups. It is likely certain individuals may participate in more than one group. Organization and leadership of each team should be decided in preparatory phases, before any major decisions are made. The Care Pathway Development Team (hereafter simply referred to as “Team”) is organized into three main sub-groups.

4.2.1 Core Group

These individual are self-nominated based on their interest in a Care Pathway topic. They have expertise related to the Care Pathway's content, both clinical (e.g., practice specialty) or scientific (e.g., pharmacology, economics) and/or represent the target audience. The Core Group submits the initial application for Care Pathway Development to the Care Pathways Committee. After preliminary approval of a Pathway application, the Core Group recruits additional Team members. The Core Team and additional members then re-organize (Working Groups and Panel) in order to pursue the next steps of Care Pathway development.

4.2.2 Working Groups

Core Group members participate in the working groups, along with the additional individuals recruited by them who reflect the characteristics described above in 4.2.

The Working Groups (or in some instances, individuals from a working group) are tasked with specific aspects of Care Pathways development. Some *suggestions* for Working Groups--or for assignment of responsibilities to certain individuals--are:

(a) Evidence Group responsible for literature search, quality assessment of existing systematic reviews (or conducting a new systematic review if needed), evidence synthesis, and GRADE rating. Methodologic and statistical experts are recommended participants for this group.

(b) Editorial Group responsible for writing and editing the final version of the Care Pathways and summaries published on the AACPDM's website as well as management of any related publications (i.e., new systematic reviews, submission of Care Pathway to a peer reviewed journal). Editorial responsibilities can be delegated to individuals within both the Evidence Group and Panel.

(c) Administrative Group responsible for producing, distributing, and organizing documentation (including meeting minutes), scheduling meetings and video or teleconferences, and managing communications with consumers and stakeholders. Administrative responsibilities can be delegated to individuals within both the Evidence Group and Panel.

4.2.3 Care Pathway Panel

Participants on the Panel are identified at the same time as the Working Groups are organized (see Part 2, PHASE III, below). The Panel includes content and/or scientific experts, stakeholders, and consumers. They are responsible for determining the scope of the Pathway topic, generating key questions, prioritizing outcomes, considering values and preferences, and for the development of the recommendation (s) of the Care Pathway and its (their) presentation.

4.3 Consumers and stakeholders

Care Pathway development should involve consumers and stakeholders in a meaningful way and avoid tokenism. It is expected that a majority of the Care Pathway Development Team, including the Panel, will be comprised of health care providers who will be end user of and/or have an interest in the outcome of the Pathway; as such, they will likely represent key stakeholder groups. However, other potential stakeholders (e.g., other types of clinicians or specialists) and/or consumers (e.g., patients and caregivers) should be identified and invited to contribute to Care Pathway development. They will participate in the specific decision-making tasks described above in the description of the Panel. As described in the steps of the GDC-CP, these participants are also required to submit COI

disclosures; in addition, they should receive adequate training in order to promote meaningful participation in the Panel's tasks.

Additional input from stakeholders and consumers will occur during external review of a draft of the Care Pathway. Specific plans for external review should be determined early on in a Care Pathway's development process. External review should involve a variety of relevant stakeholders including clinicians (e.g., AACPDM general membership), related professional organizations, advocacy groups, and patients and caregivers. A draft of the Care Pathway will be made available to these individuals and groups for a 30-day comment period. The Care Pathway Development Team should consider all comments and record the rationale for modifying or not modifying a Care Pathway in response to the comments.

4.4 Care Pathway Update Team

A review of each Pathway for updating and potential revisions is required every 5 years following the original or latest posting date. The 5 year review will always result in an update of the evidence search and GRADE evidence profiles. It may also require a revision of the Care Pathway's recommendations. More details about the process of the 5 year review are found in Part 2, PHASE X.

Members of the original Care Pathway Development Team will be asked to participate in the 5 year review by the Team or Panel Lead. New members will be recruited if required (see 4.2 for recommended participants). The Pathway Update Team can choose a new Team Lead (or Leads for specific Groups) and must establish the roles and responsibilities of all involved in the review process (see Part 2, PHASE III below).

PART 2. SPECIFIC PROCESSES FOR CARE PATHWAYS DEVELOPMENT

The AACPDM Care Pathways development process is described by 10 distinct PHASES, which are listed below. The PHASES consolidate the GDC-CP which serves as a detailed protocol. Because of the need to cross-reference this general instructional document and the Checklist, PHASES are designated by roman numerals, while Topics and Steps of the Checklist are designated by whole numbers. Note the PHASES cover all 18 Checklist Topics; however, they do not correspond numerically as some PHASES involve multiple Checklist Topics/Steps.

PHASE I: Care Pathway Application

An application to request permission to develop an AACPDM Care Pathway is submitted to the Care Pathways Committee through the AACPDM office. The application is submitted by the members of the Core Group and includes:
1) Outline of goals and objectives;
2) Timeline;
3) COI Disclosure Forms for all Core Group members;
4) Documentation of completion of the following GDC-CP items:
Topic 1: Steps 2 7, 9, 11
Topic 2: Steps 5, 6
Topic 3: Steps 1, 2
Topic 5: Step 1
Topic 6: Steps 1, 2, 3
Topic 7: Steps 1-5, 7
Topic 8: Steps 1

PHASE II: Application Review

Applications are reviewed by the Care Pathways Committee. The Committee evaluates and votes on applications that are scored/ranked using the following criteria:
-Topic priority and other considerations listed above in Section 2
-Readiness of the applicant Team
-Overall application quality, which includes completeness, resources, diversity of members and precision of topic.
-Potential COI issues and plan for mitigation

The highest-ranking applications are *preliminarily* approved for Care Pathway development under the imprimatur of the AACPDM. Of note, the AACPDM Board of Directors has created an AACPDM Care Pathway Development Grant. If interested, applicants should contact the Committee to determine if funding is available for new Pathway development. The Core Group should indicate on the application form if they wish to be considered for this funding, if available. The AACPDM Care Pathways Committee will adjudicate any requests for funding.

PHASE III: Team Preparation (also applies to Care Pathway Update Teams)

After preliminary approval, the Core Group will recruit additional Care Pathway Team members. Care Pathway Update teams may also need to recruit additional members. Development and Update Teams should address the required preparation and organization identified below in Topics 1-14 of the GDC-CP. This will involve designation of the Care Pathways Panel as they are responsible for many activities essential for the eventual formulation (or revision) of Pathway recommendations, including establishing the scope of the Care Pathway topic, generating key questions, and identifying and ranking importance of outcomes.

For final approval of a new Pathway (or 5-year review), the Development (or Update) Team should submit:
1) COI disclosure forms for all Team members if not submitted in PHASE I (GDC-CP Topic 7, step 7)
2) Any updates to objectives and/or timeline submitted in PHASE I for new Pathways; Update Teams should submit a timeline to meet 5-year deadline.
3) Documentation of completion of the following GDC-CP items:
Topic 1: Steps 8, 10
Topic 3: Steps 2-6
Topic 4. Steps 1-10
Topic 5. Steps 2-6
Topic 6. Steps 3- 8
Topic 7: Steps 1-5, 7
Topic 8. Steps 2-13
Topic 9. Steps 1 -9
Topic 14: Step 7

PHASE IV: Initial Application (or 5 Year Review) Approval

The Care Pathway Development or Update Teams will submit their PHASE III materials for review by the Care Pathways Committee. If approved, the Team then proceeds with PHASE V of Care Pathway development (or update). Alternatively, the Committee may ask the Team for protocol clarification or refinement and then re-review.

PHASE V: Evidence Search and Appraisal

Complete Steps 1-4 of GDC-CP Topic 10.
GRADE methodology (based on work by the Cochrane Collaboration) is used for any original or updated SR's undertaken to inform Care Pathways. GRADE methodology allows reporting on the certainty of effect for multiple outcomes from a body of evidence. However, it is likely original research studies included in systematic reviews developed using GRADE will not provide evidence regarding every outcome. For example, randomized controlled trials may provide the evidence for benefits, while observational studies provide the evidence for adverse effects.

Each key question posed by the Care Pathway Panel requires a separate, specific systematic search for evidence. Systematic reviews identified in the search require additional evaluation. For each key

question, evidence from existing systematic review(s) can be used for Evidence Synthesis (PHASE VI) if 1) it provides the necessary information to formulate GRADE evidence summaries and ability to rate the quality of the evidence using GRADE; 2) it was published within the last 5 years; AND 3) It meets quality standards. For systematic reviews or meta-analyses of interventions, it/they should be rated as moderate or high-quality using AMSTAR 2. Overviews of reviews should be evaluated with PRIOR. For non-intervention systematic reviews (e.g., diagnostic, prognostic), quality should be based on reporting compliance with corresponding PRISMA extensions along with use of ROBIS. The Evidence Group must perform their own quality assessments and not depend on the authors' self-reported AMSTAR 2 (or other quality appraisal tool) ratings, nor on their assurances that PRISMA reporting guidelines were followed.

Details of all existing systematic review quality appraisals must be performed independently by at least 2 members of the Evidence Group who have adequate methodologic expertise. If there are discrepancies that cannot be resolved by discussion, a third Evidence Group member must be involved in order to achieve consensus. All individual and consensus quality appraisals of existing systematic reviews used in evidence syntheses must be documented and included in the final Care Pathway report.

Based on the appraisal of existing systematic reviews, there are three potential ways to proceed with obtaining evidence. The following PHASE V categories describe these methods. Because evidence available to answer each of the key questions will vary in quality and date of publication, it may be necessary to complete more than one of these PHASE V categories.

PHASE V-existing: ***Existing Systematic Review(s)***
If all criteria regarding existing systematic reviews described above (PHASE V) are met, complete Steps 8, 9, and 10 of GDC-CP Topic 10. Note: The date of the last evidence search in each systematic review used for Pathway development (or 5-year review) should be within 12 months of posting (or re-posting) of the Pathway. The systematic review(s) (unless last search within 12 months) may require updating.

PHASE V-updated: Updated Systematic Review(s)
An existing systematic review using GRADE and meeting quality standards but published more than 5 years ago can be updated. Complete Steps 5, 8, 9, and 10 of GDC-CP Topic 10. Note: The date of the last evidence search in each systematic review used for Pathway development (or 5-year review) should be within 12 months of posting of the Pathway. The systematic review(s) (unless last search within 12 months) may require additional updating.

PHASE V-new: New Systematic Review(s)
If criteria regarding existing systematic review(s) are not met, a new systematic review(s) is/are required for the corresponding key question(s). It should be comprehensive and follow the PRISMA-P reporting guidelines, including protocol registration and preparation for peer-reviewed publication. GRADE methodology will be used to develop the new systematic review. This will facilitate both synthesis of the evidence (PHASE VI), which must be included in the systematic review, and the formulation of a recommendation or recommendations (PHASE VII) which is/are included in the Care

Pathway but not in the systematic review. It is expected that any new systematic review(s) undertaken by the Care Pathways Team will be submitted for publication in a peer-reviewed journal. After the new systematic review(s) is (are) completed, complete Steps 8, 9, and 10 of GDC-CP Topic 10. Note: The date of the last evidence search in each systematic review used for Pathway development (or 5-year review) should be within 12 months of posting (or re-posting) of the Pathway. The systematic review(s) (unless last search within 12 months) may require updating.

PHASE VI: Evidence Synthesis and Quality Rating

Complete the steps listed under GDC-CP Topics 11 and 12.
New or revised systematic reviews undertaken by Care Pathway Teams should present the evidence as recommended by GRADE using evidence summaries and evidence syntheses.

Evidence summaries are required for each comparison of treatment strategies (including no treatment or usual care). These are presented by tables that list the primary studies and their Risk of Bias assessments (shown as red for high, green for low, and yellow for some or moderate), reported effects and effect sizes, and diagrams displaying statistical (e.g., forest plot) or non-statistical (e.g., combining P-values) syntheses of quantitative intervention effects (See Appendix II-A).

Syntheses of evidence are presented in two formats: Evidence Profiles and Summary of Findings Tables (See Appendix II- B and II-C). Both types of syntheses are organized by the outcomes designated as critical or important, including evidence about harmful effects. Contents differ based on the intended audience (see table below). GRADE Evidence profiles are always included in the systematic review. They provide a detailed understanding of the judgments determining the certainty in the evidence for each outcome; as such, they are essential for consideration by Care Pathway Panels in their development of recommendations. Summary of Findings tables, based on the Evidence Profiles, are useful for a broader audience, including end users of systematic reviews and Care Pathways.

Comparison of the Content of Evidence profiles and Summary of findings tables\
(From Santessa et. al. J Clin Epidemiology 2016)

Evidence profile	**Summary of findings table**
-More detailed summary of findings	-Compact summary of findings
-Patient important outcomes	-Patient important outcomes
-Relative and absolute effect estimates	-Relative and absolute effect estimates
-Detailed judgments about certainty in the evidence for each domain separately and across domains with associated explanations, for example, detailed judgments about the indirectness of the evidence	-Judgments about certainty in the evidence as explanations
-Certainty, quality, or strength of the evidence	-Overall certainty, quality, or strength of the evidence
-Number of events and participants in the intervention and control groups	-Total number of participants and studies
-Importance of outcome	-Interpretation and additional comments to facilitate interpretation

PHASE VII: Formulating Recommendations

Complete the steps listed under GDC-CP Topics 13 and 14.

PHASE VIII: Reporting and Peer Review

Complete the Steps listed under GDC-CP Topic 15.

Comments from stakeholder and consumers who participate in the external review process will be recorded and reviewed (See GDC Topic 15, Item 7 for details). A record of the comments and the Panel's replies to them will be included in the final Care Pathway report.

Appeals filed after posting of the Pathway will be reviewed by the Care Pathways Chair, Methodology Sub-committee chair, and Care Pathway Team Lead(s) and Liaison. If the appeal reveals an error in the Care Pathway, then corrective actions will be taken by the Pathway Team with oversight by the Committee and Liaison. If it does not involve an error, a transparent explanation as to why the Pathway will not be amended will be sent by the Pathway Lead(s) to the party who filed the appeal. All comments and replies made during the 30-day external review and comments or appeals and replies made after posting will be made public on the Care Pathways webpages.

PHASE IX: Dissemination, Evaluation, and Use

Many of steps under GDC-CP Topic 16 and 17 are directed by the Care Pathways Committee. Care Pathway Development Teams should review the steps under these topics for suggestions on how they can contribute to dissemination and evaluation processes. Teams are encouraged to consider these processes during Pathway development, and actively pursue these processes as much as possible after a Pathway is posted.

PHASE X: Updating

General Instructions

For each Care Pathway, the original posting date, date of last systematic evidence search, and date for a 5-year review must be displayed on the AACPDM Care Pathway website.

The entire review process, including any necessary updates and/or revisions, must be completed by 5 years following the last online posting of the Care Pathway. Two designated Team members will contact the AACPDM Care Pathways Committee prior to the due date to initiate the review. At that time, the AACDPM website will indicate the status of the Care Pathway as "under 5-year review". If a Care Pathway review is not completed by 5 years after the original or latest online posting, it will be removed by the AACPDM staff until the review is completed.

The systematic review(s) used to develop the original (or most recent) Care Pathway will be updated (following Steps outlined in Topic 10). The searches for evidence should cover the time period after the original or most recent posting of the Care Pathway. The Update Team evaluates the new evidence to determine its impact on the Pathway's recommendations. Note all, some, or none of the recommendations included in the Care Pathway may need revision at each 5-year review.

After a Care Pathway's 5-year review is completed, the AACPDM office will update its webpage content, posting date, date of last evidence search, and date for the next 5 year review. The AACPDM membership will be notified of the update by a blast email.

Specific Requirements for Updating

***For original Care Pathway Development Teams*:** Complete Topic 18, Steps 2 and 6.

For Care Pathway Update Teams:

PHASE III: Team Preparation
Update Teams must address GDC-CP Topic 18, Step 3 which involves completing the required preparatory steps of PHASE III.

PHASE IV: 5 Year Review Approval
Documentation of completion of PHASE III is reviewed by the Committee; after it is approved, Update Teams can proceed with a new search of the evidence.

PHASE V: Evidence Search and Appraisal
Complete Steps 1-10 of GDC-CP Topic 10.

PHASE VI: Evidence Synthesis and Quality Rating
-If GRADE not used originally for a Care Pathway, the Update Team will develop a new systematic review using GRADE (complete GDC-CP Topics 11 and 12).
-If GRADE used for the original Care Pathway, the new evidence found in PHASE V is appraised and incorporated into the previous evidence summaries (complete GDC-CP Topics 11 and 12).

***PHASE VII:* Formulating Recommendations**
-If GRADE not used originally for a Care Pathway, the Update Team will complete steps of GDC-CP Topics 13 and 14.
-GRADE used for the original Care Pathway: If new evidence is available that can potentially impact the quality rating of the evidence and/or strength of the recommendation(s), the Update Team must reconvene a Care Pathway Panel to re-formulate the recommendation(s) (GDC-CP Topics 13 and 14)

PHASE IX: Reporting and Peer Review
Presentation and reporting items (GDC-CP Topic 15, Steps 1 and 2) produced by the Update Team will be submitted to the Care Pathways Committee for internal review. An external peer review process is necessary if any revisions are made to the Pathway's recommendations (GDC-CP Topic 15, Step 7). After undergoing internal review (and external review if required), the updated and/or revised Care Pathway, including all presentation and reporting items, is posted on the Care Pathways webpages.

PHASE X: Updating
The Update Team must complete Topic 18, Steps 2 and 6 to ensure the process for the next 5-year review is set in motion.

APPENDIX I: GRADE Publications

2008: Series of 6 articles published in the British Medical Journal. They describe GRADE approach to developing and presenting recommendations for management of patients. Audience for these articles is the clinician and policy-making users of GRADE's output, which includes evidence profiles, summary of findings tables, and graded recommendations

Guyatt, G.H., Oxman, A.D., Vist, G.E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P. et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008; 336: 924–926

Guyatt, G.H., Oxman, A.D., Kunz, R., Vist, G.E., Falck-Ytter, Y., and Schunemann, H.J. What is "quality of evidence" and why is it important to clinicians?. BMJ. 2008; 336: 995–99

Guyatt, G.H., Oxman, A.D., Kunz, R., Falck-Ytter, Y., Vist, G.E., Liberati, A. et al. Going from evidence to recommendations. BMJ. 2008; 336: 1049–1051

Schunemann, H.J., Oxman, A.D., Brozek, J., Glasziou, P., Jaeschke, R., Vist, G.E. et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ. 2008; 336: 1106–1110

Guyatt, G.H., Oxman, A.D., Kunz, R., Jaeschke, R., Helfand, M., Liberati, A. et al. Incorporating considerations of resources use into grading recommendations. BMJ. 2008; 336: 1170–1173

Jaeschke, R., Guyatt, G.H., Dellinger, P., Schunemann, H., Levy, M.M., Kunz, R. et al. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. (a744)BMJ. 2008; 337

2011-19: Series of 20 articles in Journal of Clinical Epidemiology. Audience is systematic review and health technology assessment authors, and guideline panelists and methodologists who provide support for guideline panels. They provide detailed guidance for those responsible for producing evidence profiles, summary of findings tables, and graded recommendations using GRADE.

Guyatt, G., Oxman, A., Akl, E., Kunz, R., Vist, G., Brozek, J. et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011; 64: 383–394

Guyatt, G., Oxman, A., Kunz, R., Atkins, D., Brozek, J., Vist, G. et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol. 2011; 64: 395–400

Balshem, H., Helfand, M., Schunemann, H.J., Oxman, A.D., Kunz, R., Brozek, J. et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011; 64: 401–406

]Guyatt, G.H., Oxman, A.D., Vist, G., Kunz, R., Brozek, J., Alonso-Coello, P. et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). J Clin Epidemiol. 2011; 64: 407–415

Guyatt, G.H., Oxman, A.D., Montori, V., Vist, G., Kunz, R., Brozek, J. et al. GRADE guidelines: 5. Rating the quality of evidence-publication bias. J Clin Epidemiol. 2011; 64: 1277–1282

Guyatt, G., Oxman, A.D., Kunz, R., Brozek, J., Alonso-Coello, P., Rind, D. et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. J Clin Epidemiol. 2011; 64: 1283–1293

Guyatt, G.H., Oxman, A.D., Kunz, R., Woodcock, J., Brozek, J., Helfand, M. et al. GRADE guidelines: 7. Rating the quality of evidence-inconsistency. J Clin Epidemiol. 2011; 64: 1294–1302

Guyatt, G.H., Oxman, A.D., Kunz, R., Woodcock, J., Brozek, J., Helfand, M. et al. GRADE guidelines: 8. Rating the quality of evidence-indirectness. J Clin Epidemiol. 2011; 64: 1303–1310

Guyatt, G.H., Oxman, A.D., Sultan, S., Glasziou, P., Akl, E.A., Alonso-Coello, P. et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011; 64: 1311–1316

Brunetti, M., Shemilt, I., Pregno, S., Vale, L., Oxman, A., Lord, J. et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. J Clin Epidemiol. 2013; 66: 140–150

Guyatt, G.H., Oxman, A.D., Sultan, S., Brozek, J., Glasziou, P., Alonso-Coello, P. et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol. 2013; 64: 151–157

Guyatt, G.H., Oxman, A.D., Santesso, N., Helfand, M., Vist, G., Kunz, R. et al. GRADE guidelines: 12. Preparing summary of findings tables: binary outcomes. J Clin Epidemiol. 2013; 66: 158–172

Guyatt, G.H., Thorlund, K., Oxman, A.D., Walter, S., Patrick, D., Furukawa, T.A. et al. GRADE guidelines: 13. Preparing summary of findings tables: continuous outcomes. J Clin Epidemiol. 2013; 66: 173–183

Andrews, J., Guyatt, G., Oxman, A.D., Alderson, P., Dahm, P., Falck-Ytter, Y. et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013; 66: 719–725

Andrews J et. al.. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength J Clin Epidemiol. 2013; 66: 726–735

Schunemann H et. al, GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health J Clin Epidemiol. 2016; 76: 89-98

Zhang, Y et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. Journal of Clinical Epidemiology 2019;111: 105-114

Zhang Y, et al. GRADE Guidelines: 19. Assessing the certainty of evidence in the importance of outcomes or values and preferences—Risk of bias and indirectness. J Clin Epidemiol. 2019;111:94-104.

Zhang, Yuan et al. GRADE guidelines: 20. Assessing the certainty of evidence in the importance of outcomes or values and preferences—inconsistency, imprecision, and other domains. J Clin Epidemiol. 2019;111:83-93.

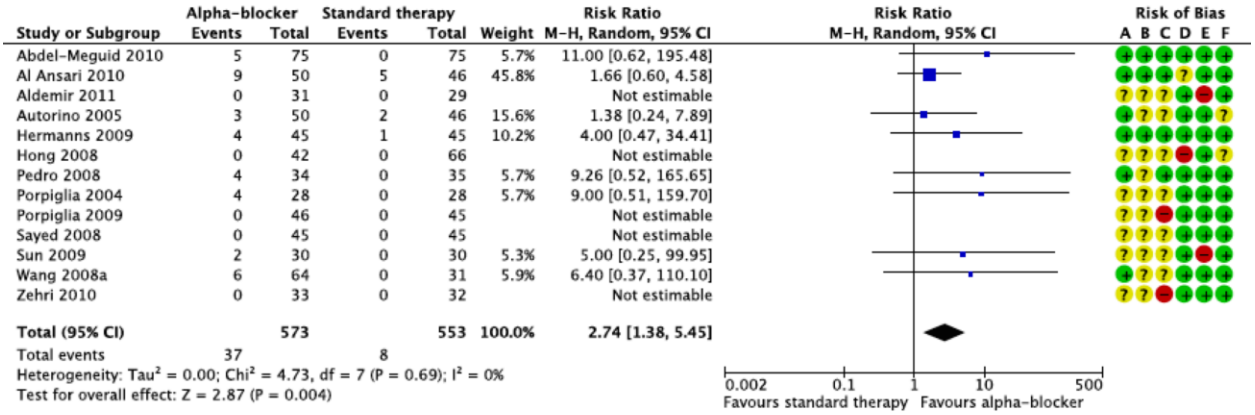
2016-present: GRADE EtD framework

Provides structure to guidelines panel meetings, and ensures that the panelists consider all established formal GRADE criteria as they decide on the recommendation text, strength, and direction (for or against an intervention).

Schunemann H et al, GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health J Clin Epidemiol. 2016; 76: 89-98

Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl E, et al. GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: 2. Clinical practice guidelines. BMJ 2016;353:i2089.

APPENDIX II-A: Examples of GRADE evidence summaries

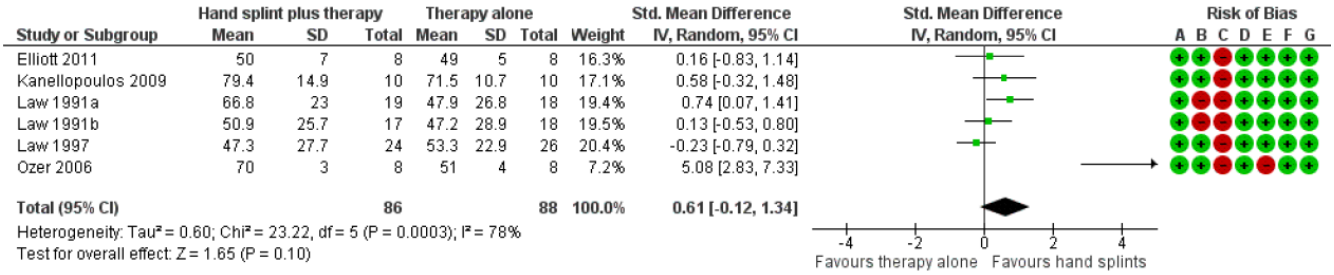


Study or Subgroup	Alpha-blocker Events	Alpha-blocker Total	Standard therapy Events	Standard therapy Total	Weight	Risk Ratio M-H, Random, 95% CI
Abdel-Meguid 2010	5	75	0	75	5.7%	11.00 [0.62, 195.48]
Al Ansari 2010	9	50	5	46	45.8%	1.66 [0.60, 4.58]
Aldemir 2011	0	31	0	29		Not estimable
Autorino 2005	3	50	2	46	15.6%	1.38 [0.24, 7.89]
Hermanns 2009	4	45	1	45	10.2%	4.00 [0.47, 34.41]
Hong 2008	0	42	0	66		Not estimable
Pedro 2008	4	34	0	35	5.7%	9.26 [0.52, 165.65]
Porpiglia 2004	4	28	0	28	5.7%	9.00 [0.51, 159.70]
Porpiglia 2009	0	46	0	45		Not estimable
Sayed 2008	0	45	0	45		Not estimable
Sun 2009	2	30	0	30	5.3%	5.00 [0.25, 99.95]
Wang 2008a	6	64	0	31	5.9%	6.40 [0.37, 110.10]
Zehri 2010	0	33	0	32		Not estimable
Total (95% CI)		**573**		**553**	**100.0%**	**2.74 [1.38, 5.45]**
Total events	37		8			

Heterogeneity: Tau² = 0.00; Chi² = 4.73, df = 7 (P = 0.69); I² = 0%
Test for overall effect: Z = 2.87 (P = 0.004)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

EXAMPLE: Hand splints for children with cerebral palsy
Outcome: Upper limb skill (immediate: 3-6 months of splint wearing)



Study or Subgroup	Hand splint plus therapy Mean	SD	Total	Therapy alone Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Elliott 2011	50	7	8	49	5	8	16.3%	0.16 [-0.83, 1.14]
Kanellopoulos 2009	79.4	14.9	10	71.5	10.7	10	17.1%	0.58 [-0.32, 1.48]
Law 1991a	66.8	23	19	47.9	26.8	18	19.4%	0.74 [0.07, 1.41]
Law 1991b	50.9	25.7	17	47.2	28.9	18	19.5%	0.13 [-0.53, 0.80]
Law 1997	47.3	27.7	24	53.3	22.9	26	20.4%	-0.23 [-0.79, 0.32]
Ozer 2006	70	3	8	51	4	8	7.2%	5.08 [2.83, 7.33]
Total (95% CI)			**86**			**88**	**100.0%**	**0.61 [-0.12, 1.34]**

Heterogeneity: Tau² = 0.60; Chi² = 23.22, df = 5 (P = 0.0003); I² = 78%
Test for overall effect: Z = 1.65 (P = 0.10)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

APPENDIX II-B. Examples of GRADE Evidence Profile

Appendix 8: GRADE assessment, by outcome

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBD	standard care	Relative (95% CI)	Absolute (95% CI)		
Randomized controlled trials												
Seizure freedom (total seizures) (treatment duration: 14 weeks; number of patients with zero seizures during treatment)												
1	randomised trials	not serious	not serious	not serious	very serious [a,b,c]	none	3/61 (4.9%)	0/59 (0.0%)	**RR 6.77** (0.36 to 128.38) [d]	—	⊕⊕◯◯ LOW	CRITICAL
Total seizure frequency (treatment duration: 14 weeks; median % reduction in monthly seizures from baseline)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	296	220	-	**−19.8%** (−27.0% to −12.6%)	⊕⊕⊕◯ MODERATE	
Tonic-clonic seizure frequency (treatment duration: 14 weeks; median % reduction in monthly seizures from baseline)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	219	171	-	**−26.7%** (−38.6% to −14.6%)	⊕⊕⊕◯ MODERATE	
Treatment response (treatment duration: 14 weeks; number of participants with at least a 50% reduction in total seizures from baseline)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	32/86 (37.2%)	18/85 (21.2%)	**RR 1.76** (1.07 to 2.88)	**161 more per 1,000** (from 15 more to 398 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Quality of life (child) (treatment duration: 14 weeks; Quality of Life in Childhood Epilepsy Scale, range: 0 to 100)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	296	220	-	MD **0.6 higher** (2.6 lower to 3.9 higher)	⊕⊕⊕◯ MODERATE	
Sleep disruption (treatment duration: 14 weeks; Sleep Disruption Rating Scale; range: 0 to 10)												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	296	220	-	MD **0.3 lower** (0.8 lower to 0.2 higher)	⊕⊕⊕◯ MODERATE	
Status epilepticus (treatment duration: 12 weeks; number of children with status epilepticus during the treatment period)												

Question: Low-dose computed tomography (LDCT) compared to usual care in current and recent former smokers
Setting: health system
Bibliography: Ali MU, Miller J, Peirson L, Fitzpatrick-Lewis D, Kenny M, Sherifali D, & Raina P. (2016). Screening for lung cancer: A systematic review and meta-analysis. Preventive Medicine 89: 301-14. Gareen IF, Duan F, Greco EM, Snyder BS, Boiselle PM, Park ER... & Gatsonis C. (2014). Impact of lung cancer screening results on participant health-related quality of life and state anxiety in the National Lung Screening Trial. Cancer 120(21): 3401-09. Mazzone PJ, Obuchowski N, Fu AZ, Philipps M, & Meziane M. (2013). Quality of life and healthcare use in a randomized controlled lung cancer screening study. Annals of the American Thoracic Society 10(4): 324-329.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	low-dose computed tomography (LDCT)	usual care	Relative (95% CI)	Absolute (95% CI)		
Lung cancer mortality (follow up: range 4 years to 8 years)												
4	randomised trials	not serious	serious [a]	not serious [b]	not serious	none	442/31228 (1.4%)	516/31693 (1.6%)	**RR 0.86** (0.76 to 0.97)	**228 fewer per 100,000** (from 391 fewer to 49 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
All-cause mortality (follow up: range 4 years to 8 years)												
4	randomised trials	not serious	serious [a]	not serious [b]	serious [c]	none	2149/31228 (6.9%)	2238/31693 (7.1%)	**RR 0.96** (0.91 to 1.02)	**282 fewer per 100,000** (from 636 fewer to 141 more)	⊕⊕◯◯ LOW	CRITICAL
Early stage at diagnosis (Grade I - IIb) (follow up: range 4 years to 8 years)												
3	randomised trials	not serious	not serious	not serious [b]	not serious	none	678/1169 (58.0%)	385/987 (39.0%)	**RR 1.48** (1.35 to 1.62)	**18,723 more per 100,000** (from 13,652 more to 24,184 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Major complications due to false positives												
1	observational studies	not serious	not serious	not serious [d,e]	not serious	strong association [f]	18/1000 (1.8%)	0/1000 (0.0%)	not estimable	**1,800 more per 100,000** (from 1,000 more to 2,600 more)	⊕⊕⊕◯ MODERATE	CRITICAL
False positives												
1	observational studies	not serious	not serious	not serious	not serious	none	233/1000 (23.3%)	0/1000 (0.0%)	not estimable	**23,000 more per 100,000** (from 20,700 more to 25,900 more)	⊕⊕◯◯ LOW	IMPORTANT
Quality of life (assessed with: Short-form 36, EQ-5D, UCSD SOBQ, SGRS)												
2	randomised trials	not serious	not serious	not serious [g]	not serious [h]	none	Of 2812 subjects analyzed in the NLST (Gareen 2014), no differences were found between physical or mental quality of life pre- or post-screening for participants randomized to LDCT (n=1947) or to chest x-ray (n=865). At six months post-screening, participants who had undergone LDCT saw a decrease of 2.65 points and 1.81, respectively; participants undergoing chest x-ray had a decrease of 2.95 and 2.3 points, respectively. A randomized study of NLST-eligible subjects (Mazzone 2013) did not identify a difference in quality of life in any measures, (EQ-5D, St. George Respiratory Scores, UCSD Shortness of Breath Questionnaire) between persons screened with LDCT (n=308) and persons not receiving screening (n=320) from baseline to 6-, 12-, 18-, and 24-months follow-up.		⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations:

a. There is a high amount of heterogeneity, with some studies showing no benefit or potential harm, and another showing benefit.
b. Although there is an indirect comparator in the most heavily weighted study (NLST), this would only lead to an underestimation of the effect, which would not decrease our certainty in the estimate.
c. The confidence interval passes the threshold for clinical decision-making, from a small benefit on the one end to a small risk of potential harm on the other.
d. Data are imputed by applying the false positive rate of 23.3% to the rate of major complications in those who underwent invasive follow-up testing.
e. Of patients undergoing major invasive follow-up procedures, 700 out of 100,000 had benign conditions (underwent unnecessary procedure).
f. Large to very large relative effect estimate, increasing our certainty that major complications are associated with screening.
g. In both studies examined, there were no meaningful differences either between groups (LDCT versus chest x-ray/no screening) or from pre- to post-screening.
h. As a change of three points for Physical Component Score and Mental Component Score is considered to be a minimum clinically important change, likely no meaningful differences were observed from baseline to six months post-screening for either group in Gareen 2014.

APPENDIX II-C: Examples of GRADE Summary of Findings Table

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Botulinum toxin compared to Placebo for motor and phonic tics in Tourette's syndrome

Botulinum toxin compared to placebo for motor and phonic tics in Tourette's syndrome

Patient or population: Tourette's syndrome with motor and phonic tics
Setting: hospital
Intervention: botulinum toxin injections
Comparison: placebo injections

Outcomes	Net effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
Severity of motor tics (measured by videotape of tic count)	Median proportional change in treated tics: with Botulinum toxin -39%; with placebo +5.8%; net effect -37% (IQR -77% to -15%)	18 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1, 2]
Severity of phonic tics	Phonic tics were not measured.		
Premonitory Urge (treated tics)	The net effect for urge in treated tics was -0.94 (-1.71 to -0.17) and for premonitory sensation in treated tics was 0.03 (-0.86 to 0.92)	18 (1 RCT)	⊕⊖⊖⊖ VERYLOW [1, 2]
Sensory tics	Senory tics were not measured in this trial.		
Adverse events	There were 32 adverse events reported in the Botulinum group;with placebo group only five adverse events were reported which includes weakness and neck discomfort.	18 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1, 2]
Development of immunoresistance against botulinum toxin	This outcomes were not reported in this included study.		

Net effect: proportional change in the intervention arm - proportional change in the control arm; **CI:** confidence interval

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded one level due to indirectness: The majority of participants had a mild tic disorder, limiting the results from generalisation to everyone with Tourette's syndrome.
[2] Downgraded two levels due to very serious imprecision: Very small sample size in the study (18 participants) and wide confidence intervals.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Isopropyl alcohol compared to standard treatment for treatment of postoperative nausea and vomiting

Isopropyl alcohol compared to standard treatment for treatment of postoperative nausea and vomiting

Patient or population: patients with treatment of postoperative nausea and vomiting
Settings: Post-anaesthesia Care Areas
Intervention: Isopropyl alcohol
Comparison: Standard treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard treatment	Isopropyl alcohol				
Requirement for rescue anti-emetics	Study population[1]		RR 0.66 (0.45 to 0.98)	215 (4 studies)	⊕⊕⊝⊝ low[2,3]	
	392 per 1000	259 per 1000 (176 to 384)				
	Medium risk population[1]					
	275 per 1000	182 per 1000 (124 to 270)				
Adverse effects[4]	See comment	See comment	Not estimable	0 (0)	See comment	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Calculated using control group results.
[2] Study by Merritt (2002) was not adequately randomised.

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