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| **General information** | |
| 1. | **\*U-REACH title**  Indicate the name of your U-REACH project. |
|  | Interventions for individuals with attention-deficit/hyperactivity disorder (ADHD): an umbrella review |
| 2. | **\*Anticipated completion date**  Give the date by which the U-REACH project is expected to be completed |
|  | 01/03/2025 |
| 3. | **\*Stage of review at time of this submission**  Indicate the stage of progress of the U-REACH project (e.g., preliminary, non-systematic, searches have started). |
|  | The final search was performed on the 19th January 2025; preliminary screening has started, and the data extraction sheet has been pre-tested across two data extractor teams (piloted on 2 different meta-analyses). |
| 4. | **\*Named contacts**  The named contact acts as the guarantor for the accuracy of the information presented in the register record. |
|  | Corentin Gosling, Samuele Cortese |
| 5. | **\*Named contact email**  Give the electronic mail address of the named contact. |
|  | [corentin.gosling@gmail.com](mailto:corentin.gosling@gmail.com);samuele.cortese@soton.ac.uk |
| 6. | **\*Named contact affiliation**  Full title of the main affiliation of the named contact. |
|  | **Université Paris Nanterre, University of Southampton** |
| 7. | **\*U-REACH team members and their organisational affiliations.**  Give the title, first name, last name and main affiliation of each member of the U-REACH team. For each author, provides their contribution to the protocol. |
|  | N/A |
| 8. | **\*Funding sources/sponsors**  Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the U-REACH project, as well as their contribution to the protocol. |
|  | **Agence Nationale de la recherche (FR) and NIHR (UK)** |
| 9. | **\*Conflicts of interest**  List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the U-REACH project. |
|  | Prof. Cortese has declared reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH) in relation to lectures delivered for ACAMH, the Canadian AADHD Alliance Resource, the British Association of Psychopharmacology, Healthcare Convention and CCM Group team for educational activity on ADHD, and has received honoraria from Medice |
| 10. | **\*U-REACH objective**  State the general objective of the U-REACH project. Questions may be framed or refined using PI(E)COS where relevant. |
|  | The aim of this project is to perform a large-scale synthesis of the best available meta-analytic evidence on the effects of any intervention on key outcomes in individuals with ADHD across the lifespan |

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| **UMBRELLA REVIEW: identification of SR/NMA** | |
| 11. | **\*Databases**  State the databases/sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period). Provide the search strategy that will be used for at least one database. |
|  | **PubMed**  (("Attention Deficit Disorder with Hyperactivity"[mesh] OR "Attention Deficit and Disruptive Behavior Disorders"[Mesh:NoExp] OR "attention deficit"[tw] OR "attention deficits"[tw] OR "attention deficit\*"[tw] OR "ADHD"[tw] OR "TDAH"[tw] OR "hyperactive disorder"[tw] OR "hyperactive disorders"[tw] OR "hyperactive disorder\*"[tw] OR "hyperkinetic syndrome"[tw] OR "hyperkinetic disorder"[tw] OR "hyperkinetic disorders"[tw] OR "hyperkinetic disorder\*"[tw] OR "attention deficit"[title/abstract:~3] OR "attention deficits"[title/abstract:~3] OR "hyperactive disorder"[title/abstract:~3] OR "hyperactive disorders"[title/abstract:~3] OR "hyperkinetic syndrome"[title/abstract:~3] OR "hyperkinetic disorder"[title/abstract:~3] OR "hyperkinetic disorders"[title/abstract:~3]) AND ("Meta-Analysis"[ptyp] OR "meta analysis"[tw] OR "meta analytic"[tw] OR "meta anal\*"[tw] OR “meta-anal\*” OR "metaanalysis"[tw] OR "metaanalytic"[tw] OR "metaanal\*"[tw] OR "Cochrane database syst rev"[jour] OR "Meta-research"[tw] OR "Metaresearch"[tw] OR "Aggregate analysis"[tw] OR "Research synthesis"[tw]))  **Embase** (OVID-version)  ((exp "attention deficit disorder"/ OR exp "attention deficit disorder"/ OR exp "attention deficit hyperactivity disorder"/ OR "attention deficit".mp OR "attention deficits".mp OR "attention deficit\*".mp OR "ADHD".mp OR "TDAH".mp OR "hyperactive disorder".mp OR "hyperactive disorders".mp OR "hyperactive disorder\*".mp OR "hyperkinetic syndrome".mp OR "hyperkinetic disorder".mp OR "hyperkinetic disorders".mp OR "hyperkinetic disorder\*".mp OR (("attention" ADJ3 "deficit") OR ("attention" ADJ3 "deficits") OR ("hyperactive" ADJ3 "disorder") OR ("hyperactive" ADJ3 "disorders") OR ("hyperkinetic" ADJ3 "syndrome") OR ("hyperkinetic" ADJ3 "disorder") OR ("hyperkinetic" ADJ3 "disorders")).ti,ab) AND (exp "Meta Analysis"/ OR "meta analysis".mp OR "meta analytic".mp OR "meta anal\*".mp OR "metaanalysis".mp OR "metaanalytic".mp OR "metaanal\*".mp OR "cochrane database of systematic reviews".jn OR "Meta-research".mp OR "Metaresearch".mp OR "Aggregate analysis".mp OR "Research synthesis".mp) NOT conference review.pt)  **Emcare** (OVID version)  ((exp "attention deficit disorder"/ OR exp "attention deficit disorder"/ OR exp "attention deficit hyperactivity disorder"/ OR "attention deficit".mp OR "attention deficits".mp OR "attention deficit\*".mp OR "ADHD".mp OR "TDAH".mp OR "hyperactive disorder".mp OR "hyperactive disorders".mp OR "hyperactive disorder\*".mp OR "hyperkinetic syndrome".mp OR "hyperkinetic disorder".mp OR "hyperkinetic disorders".mp OR "hyperkinetic disorder\*".mp OR (("attention" ADJ3 "deficit") OR ("attention" ADJ3 "deficits") OR ("hyperactive" ADJ3 "disorder") OR ("hyperactive" ADJ3 "disorders") OR ("hyperkinetic" ADJ3 "syndrome") OR ("hyperkinetic" ADJ3 "disorder") OR ("hyperkinetic" ADJ3 "disorders")).ti,ab) AND (exp "Meta Analysis"/ OR "meta analysis".mp OR "meta analytic".mp OR "meta anal\*".mp OR "metaanalysis".mp OR "metaanalytic".mp OR "metaanal\*".mp OR "cochrane database of systematic reviews".jn OR "Meta-research".mp OR "Metaresearch".mp OR "Aggregate analysis".mp OR "Research synthesis".mp))  **PsycInfo**  ((DE "Attention Deficit Disorder with Hyperactivity" OR DE "Attention Deficit Disorder" OR DE "Hyperkinesis" OR TI (attention\* deficit\*) OR AB (attention\* deficit\*) OR TI (ADHD) OR AB (ADHD) OR TI (hyperkinetic disorder\*) OR AB (hyperkinetic disorder\*) OR TI (hyperkinetic syndrome\*)) OR AB (hyperkinetic syndrome\*) OR DE("attention deficits" OR "attention deficit\*" OR "ADHD" OR "TDAH" OR "hyperactive disorder" OR "hyperactive disorders" OR "hyperactive disorder\*" OR "hyperkinetic syndrome" OR "hyperkinetic disorder" OR "hyperkinetic disorders" OR "hyperkinetic disorder\*") OR SU("attention deficits" OR "attention deficit\*" OR "ADHD" OR "TDAH" OR "hyperactive disorder" OR "hyperactive disorders" OR "hyperactive disorder\*" OR "hyperkinetic syndrome" OR "hyperkinetic disorder" OR "hyperkinetic disorders" OR "hyperkinetic disorder\*") OR TI("attention deficits" OR "attention deficit\*" OR "ADHD" OR "TDAH" OR "hyperactive disorder" OR "hyperactive disorders" OR "hyperactive disorder\*" OR "hyperkinetic syndrome" OR "hyperkinetic disorder" OR "hyperkinetic disorders" OR "hyperkinetic disorder\*") OR AB("attention deficits" OR "attention deficit\*" OR "ADHD" OR "TDAH" OR "hyperactive disorder" OR "hyperactive disorders" OR "hyperactive disorder\*" OR "hyperkinetic syndrome" OR "hyperkinetic disorder" OR "hyperkinetic disorders" OR "hyperkinetic disorder\*") OR (("attention" N3 "deficit") OR ("attention" N3 "deficits") OR ("hyperactive" N3 "disorder") OR ("hyperactive" N3 "disorders") OR ("hyperkinetic" N3 "syndrome") OR ("hyperkinetic" N3 "disorder") OR ("hyperkinetic" N3 "disorders"))) AND (DE "meta analysis" OR DE "meta-analysis" OR DE "systematic review" OR TI (meta analy\*) OR AB (meta analy\*) OR DE("meta analysis" OR "meta-analysis" OR "meta analytic" OR "meta anal\*" OR "metaanalysis" OR "metaanalytic" OR "metaanal\*" OR "cochrane database of systematic reviews".jn OR "Meta-research" OR "Metaresearch" OR "Aggregate analysis" OR "Research synthesis") OR SU("meta analysis" OR "meta-analysis" OR "meta analytic" OR "meta anal\*" OR "metaanalysis" OR "metaanalytic" OR "metaanal\*" OR "cochrane database of systematic reviews".jn OR "Meta-research" OR "Metaresearch" OR "Aggregate analysis" OR "Research synthesis") OR TI("meta analysis" OR "meta-analysis" OR "meta analytic" OR "meta anal\*" OR "metaanalysis" OR "metaanalytic" OR "metaanal\*" OR "cochrane database of systematic reviews".jn OR "Meta-research" OR "Metaresearch" OR "Aggregate analysis" OR "Research synthesis") OR AB("meta analysis" OR "meta-analysis" OR "meta analytic" OR "meta anal\*" OR "metaanalysis" OR "metaanalytic" OR "metaanal\*" OR "cochrane database of systematic reviews".jn OR "Meta-research" OR "Metaresearch" OR "Aggregate analysis" OR "Research synthesis")))  **Web of Science**  ((TI=("attention deficits" OR "attention deficit\*" OR "ADHD" OR "TDAH" OR "hyperactive disorder" OR "hyperactive disorders" OR "hyperactive disorder\*" OR "hyperkinetic syndrome" OR "hyperkinetic disorder" OR "hyperkinetic disorders" OR "hyperkinetic disorder\*" OR ("attention" NEAR/3 "deficit") OR ("attention" NEAR/3 "deficits") OR ("hyperactive" NEAR/3 "disorder") OR ("hyperactive" NEAR/3 "disorders") OR ("hyperkinetic" NEAR/3 "syndrome") OR ("hyperkinetic" NEAR/3 "disorder") OR ("hyperkinetic" NEAR/3 "disorders")) OR AB=("attention deficits" OR "attention deficit\*" OR "ADHD" OR "TDAH" OR "hyperactive disorder" OR "hyperactive disorders" OR "hyperactive disorder\*" OR "hyperkinetic syndrome" OR "hyperkinetic disorder" OR "hyperkinetic disorders" OR "hyperkinetic disorder\*" OR ("attention" NEAR/3 "deficit") OR ("attention" NEAR/3 "deficits") OR ("hyperactive" NEAR/3 "disorder") OR ("hyperactive" NEAR/3 "disorders") OR ("hyperkinetic" NEAR/3 "syndrome") OR ("hyperkinetic" NEAR/3 "disorder") OR ("hyperkinetic" NEAR/3 "disorders")) OR AK=("attention deficits" OR "attention deficit\*" OR "ADHD" OR "TDAH" OR "hyperactive disorder" OR "hyperactive disorders" OR "hyperactive disorder\*" OR "hyperkinetic syndrome" OR "hyperkinetic disorder" OR "hyperkinetic disorders" OR "hyperkinetic disorder\*" OR ("attention" NEAR/3 "deficit") OR ("attention" NEAR/3 "deficits") OR ("hyperactive" NEAR/3 "disorder") OR ("hyperactive" NEAR/3 "disorders") OR ("hyperkinetic" NEAR/3 "syndrome") OR ("hyperkinetic" NEAR/3 "disorder") OR ("hyperkinetic" NEAR/3 "disorders"))) AND (TI=("meta-analy\*" OR "metaanaly\*" OR "Meta-research" OR "Metaresearch" OR "Aggregate analysis" OR "Research synthesis") OR AB=("meta analy\*" OR "metaanaly\*" OR "Meta-research" OR "Metaresearch" OR "Aggregate analysis" OR "Research synthesis") OR AK=("meta analy\*" OR "metaanaly\*" OR "Meta-research" OR "Metaresearch" OR "Aggregate analysis" OR "Research synthesis")))  **Cochrane Library**  ("attention deficits" OR "attention deficit\*" OR "ADHD" OR "TDAH" OR "hyperactive disorder" OR "hyperactive disorders" OR "hyperactive disorder\*" OR "hyperkinetic syndrome" OR "hyperkinetic disorder" OR "hyperkinetic disorders" OR "hyperkinetic disorder\*" OR ("attention" NEAR/3 "deficit") OR ("attention" NEAR/3 "deficits") OR ("hyperactive" NEAR/3 "disorder") OR ("hyperactive" NEAR/3 "disorders") OR ("hyperkinetic" NEAR/3 "syndrome") OR ("hyperkinetic" NEAR/3 "disorder") OR ("hyperkinetic" NEAR/3 "disorders")):ti,ab,kw  **More information**  The searches on these databases will be completed with manual searches; experts in the field will be contacted to identify any additional potentially relevant references. |
| 12. | **\*Types of reviews to be included**  Give details of the type of evidence synthesis (systematic review, pairwise meta-analysis, and/or network meta-analysis) eligible for inclusion in the U-REACH project. |
|  | **Study Designs for Inclusion**   * Systematic reviews with meta-analysis of randomized controlled trials (RCTs), including:   + Pairwise meta-analyses (PWMA)   + Network meta-analyses (NMA)   + Individual participant data meta-analyses (IPD-MA) * No restrictions on language or publication date   **Methodological Requirements**   * Systematic Reviews characterized by:   + Search in at least two databases   + Clear reporting of inclusion/exclusion criteria   **Special Considerations**   * PWMA/NMA combining RCTs with non-RCTs are eligible if the results from RCTs can be reliably extracted separately * IPD-MA and NMA are eligible if the raw data is available for analysis replication, or if they present the results of a PWMA in a way allowing for their replication (such as forest plots) * Conference proceedings: Authors will be contacted for additional information if no other PWMA is available for the same PICO * Pre-publication manuscripts are eligible if they meet inclusion criteria   **Exclusion Criteria**   * Umbrella reviews (but their references will be checked) * Non-systematic reviews * Systematic reviews without meta-analysis * Dose-response meta-analyses without pooled effect sizes * Meta-regressions without pooled effect sizes * Imaging studies * Genetic studies * PhD theses * Books |
| 13. | **\*Selection and data extraction**  Describe the process that will be used for selecting the studies and for extracting the data from the reports (e.g., two independent authors for the screening, assessment of eligibility and selection of studies, and data extraction). |
|  | **Study Selection**   * Independent pairs of blind reviewers will conduct:   + Initial screening of titles and abstracts   + Full-text assessment of potentially eligible PWMA/NMA/ IPD-MA   + Final selection of included PWMA/NMA/IPD-MA   **Data Extraction**   * Independent pairs of blind reviewers will extract data from included PWMA/NMA/ IPD-MA (see the data extraction sheet attached). * All extracted data will be cross-checked for accuracy and completeness by the lead authors   **Quality Assessment**   * Independent pairs of blind reviewers will conduct AMSTAR-2 scoring for each included PWMA/NMA/IPD-MA |
| 14. | **\*Strategy for overlapping reviews**  State the selection procedure that will be used when several reviews answering the same question are available. |
|  | **Primary Analysis: Intervention vs Inactive Control Comparisons**  There may likely be PWMAs/NMAs/ IPD-MA focusing on the same PICO. In this case, a 4-level selection will be progressively implemented  **First-Level Selection: Replicable work**  We will retain only meta-analyses that provide complete data needed for replication, including effect sizes, variances or 95% confidence intervals, and sample sizes. This transparency will allow us to verify the original authors' calculations and apply a standardized framework for evidence stratification.  **Second-Level Selection: Recent Publications**  PWMA/NMA/ IPD-MA published after January 1st, 2018 will be considered with priority. This criterion will allow us to avoid outdated and hence likely less comprehensive PWMA/NMA/IPD-MA.  **Third-Level Selection: Age Group Homogeneity**  Among recent PWMA/NMAs/ IPD-MA, only those analyzing homogeneous age groups will be retained, as treatment effects vary across sage groups.  **Fourth-Level Selection: Methodological Quality**  When multiple PWMA/NMAs/ IPD-MA meet the above criteria, we will select the one with the highest methodological quality, assessed using five key AMSTAR criteria:   1. Protocol pre-registration 2. Comprehensive search strategy 3. Duplicate study selection 4. Duplicate data extraction 5. Risk of bias assessment   If several PWMA/NMAs/ IPD-MA published after January 1st 2018, with homogeneous age groups, and identical methodological quality are available, we will favor the NMA over the PWMA and IPD-MA.  **Alternative Selection Paths**  If no PWMA/NMA published after 2018 meet the primary criteria, the following hierarchical approach will be used:   1. Pre-2018 meta-analyses with homogeneous age groups 2. For cases where no PWMA/NMA/ IPD-MA with homogeneous age groups exist (regardless of publication date), selection will be based on methodological quality, with separate analyses conducted for the different age groups.   **Secondary Analysis: Head-to-head Comparisons**  **Initial Selection Criterion**  In relation to the comparison between different intervention types, selection will first identify all network meta-analyses (NMAs) with accessible raw data for calculation replication.  **Selection Hierarchy**  Among NMAs with accessible raw data:   1. Priority will be given to NMAs published after January 1st, 2018. If multiple NMAs exist in this category, selection will be based on methodological quality using AMSTAR-2 criteria 2. If no post-2018 NMAs with raw data are available, selection will be based on methodological quality regardless of publication date. |
| 15. | **\*Participants/population**  Give summary criteria for the participants or populations being studied by the U-REACH project. The preferred format includes details of both inclusion and exclusion criteria. |
|  | **Inclusion Criteria**  The synthesis will include meta-analyses focused on individuals diagnosed with attention-deficit/hyperactivity disorder (ADHD). Eligible diagnoses must be established using established diagnostic criteria from:   * Diagnostic and Statistical Manual of Mental Disorders (DSM) (Version III through 5-TR) * International Classification of Diseases (ICD) (Version 9-11) * Studies including participants with ADHD and comorbid conditions will be included, provided all participants have a confirmed ADHD diagnosis. * All age groups will be considered (preschoolers [<6 yo]; Children and adolescents [6-17 yo]; Adults [≥18 yo])   **Exclusion Criteria**  PWMA/NMA/ IPD-MA will be excluded if they include participants with unconfirmed or unclear ADHD diagnoses, such as those based on:   * Screening scale cut-off scores alone * Self-reported diagnoses * Informal diagnostic statements (e.g., "doctor said")   Additionally, meta-analyses will be excluded if they combine data from participants with confirmed and unconfirmed diagnoses in a way that prevents reliable separation of information from individual RCTs based on diagnostic status. |
| 16. | **\*Intervention(s), exposure(s)** Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed. If no specific restriction is anticipated, please try to expose the general categorization of interventions you plan to make. |
|  | **Overview**  This synthesis will examine all pharmacological and non-pharmacological interventions for ADHD identified in systematic reviews, provided they are clearly defined and distinguishable from other intervention categories.  Here are examples of interventions we expect to include:  **Pharmacological**   * Amphetamines * Methylphenidate * Atomoxetine * Alpha-2 agonists (guanfacine, clonidine) * Viloxazine * Antidepressants (e.g, bupropion, venlafaxine, desipramine) * Antipsychotics (e.g, aripiprazole, risperidone, thioridazine) * Other medications (e.g., modafinil, reboxetine, carbamazepine)   **Psychosocial interventions**   * Cognitive Behavioral Therapy (CBT) * Dialectical Behavioral Therapy (DBT) * Parent-mediated behavioral interventions * Teacher-mediated behavioral training * Child-focused behavioral therapy * Social skill training * Organizational skills interventions * Psychoeducation * Mindfulness * Relaxation therapy * Hypnotherapy   **Complementary and Alternative Medicine**   * Physical training/exercise * Dietary interventions * Neurofeedback * Transcranial magnetic stimulation (rTMS) * Transcranial direct current stimulation (tDCS) * Nutritional supplements:   + Polyunsaturated fatty acids   + Vitamin D   + Zinc   + Iron   + Carnitine * Herbal supplements:   + Asian herbal medicine   + Ginkgo biloba   + Ginseng   + Hypericum   + Pine bark extract * Acupuncture   **Intervention Classification Criteria**   * Each intervention must be clearly defined and distinguishable from other categories. * Broad, overlapping categories will be excluded, such as:   + Generic "psychosocial interventions" that combine multiple distinct approaches   + General "medication" categories that merge different pharmacological classes * Classification Validation:   + Corrected Coverage Area (CCA) analysis will be conducted using the Metaumbrella R package   + Expected overlap thresholds:     - Pharmacological interventions: <5% overlap     - Non-pharmacological interventions: <10% overlap   + If higher overlap is found:     - Intervention definitions will be revised to broader constructs where meaningful     - Or specific intervention subtypes will be removed from analysis   Note: This list is not exhaustive and may be expanded to include additional interventions identified in eligible meta-analyses, provided they meet the classification criteria. |
| 17. | **\*Comparator(s)/control**  Where relevant, give details of the alternatives against which the interventions/exposures selected in your U-REACH project will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria. |
|  | **Primary Analysis: Intervention versus inactive Control Groups**  Acceptable Control Conditions   1. Standard Inactive Controls  * Placebo pill * « Psychological » placebo * Waiting-list * Treatment as usual/standard care * Non-therapeutic activities (e.g., cooking classes) * Control groups referred to as "inactive" by the original meta-analysis authors   (however, these must not include interventions typically associated with substantial therapeutic effects, e.g.: manualized, structured psychoeducation sessions delivered by study investigators   1. Augmentation Studies Control groups, considered eligible when:  * Both experimental and control groups receive the same active intervention * The experimental group receives an additional intervention under investigation   (e.g., : in studies where both groups receive methylphenidate, but the experimental group also receives cognitive training, the control group (methylphenidate only) will be considered valid  **Secondary Analysis: Head-to-head comparisons**  The secondary analysis will focus exclusively on network meta-analyses that include direct and indirect head-to-head comparisons between interventions included in the primary analysis. |
| 18. | **\*Main outcome(s)** Give the pre-specified main outcomes of the U-REACH project, including details of how the outcomes are defined / measured, and when these measurement are made, if these are part of the inclusion criteria. If no specific restriction is anticipated, please try to expose the general categorization of outcomes you plan to make. |
|  | **Primary Outcomes**  **1. Core ADHD Symptoms**   * Combined ADHD symptoms (inattentive + hyperactive/impulsive), rated by teachers, clinicians, parents/caregivers, or self-reported   **2. Acceptability and Tolerability**   * Acceptability: all-cause discontinuation * Tolerability: discontinuation due to adverse events   Note: The core ADHD symptoms will be analyzed separately (when possible) depending on the timing of the measure: at post-test (closest 12 weeks), and, when available, closest to 26- or 52-weeks follow-up. |
| 19. | **\*Additional outcome(s)** List the pre-specified additional outcomes of the U-REACH project, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’. |
|  | **Secondary Outcomes**  **1. Functional Outcomes**   * Academic/job performance * Clinical Global Impression (CGI) rated by clinicians or parents/caregivers * Social-communication skills * Driving performance   Executive functioning  **2. Comorbid Psychopathology**   * Conduct Disorder symptoms * Oppositional Defiant Disorder symptoms * Depressive disorder symptoms * Manic symptoms * Anxiety symptoms * Learning disorder symptoms * Tics/Tourette's disorder symptoms * Emotional dysregulation * Substance use disorder symptoms and behaviors * Suicidal ideation/behavior   **3. Quality of Life**   * Quality of life (patients) * Quality of life (caregivers)   **4. Safety**   * Specific adverse events: decreased appetite and sleep problems   Note: All these outcomes will be analyzed separately (when possible) depending on the timing of the measure: at post-test (closest 12 weeks), and, when available, closest to 26- or 52-weeks follow-up. |

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| **EVALUATION of quality** | |
| 20. | **\*Assessment of the methodological quality of individual studies**  Describe the method for assessing the quality of included individual studies. |
|  | The methodological quality of individual studies will not be reassessed, and will be extracted directly or the PWMA/NMA/IPD-MA reports.  We will tailor the assessment of the methodological quality of included RCTs on the Cochrane RoB-2 tool. The following correspondence between Cochrane RoB-1 and RoB-2 will be applied:   |  |  | | --- | --- | | **Cochrane RoB-1** | **Cochrane RoB-2** | | Random sequence generation  Allocation concealment | Randomization Process | | Blinding of participants/personnel | Deviations from Intended Interventions | | Incomplete outcome data | Measurement of the Outcome | | Incomplete outcome data | Missing Outcome Data | | Selective reporting | Selection of the Reported Result | |
| 21. | **\*Assessment of the methodological quality of SR/NMA**  Describe the method for assessing the quality of included SR/NMA. |
|  | The methodological quality of included PWMA/NMA/IPD-MA will be assessed using the AMSTAR-2 tool (again, by blind pairs of reviewers). |

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| **ANALYSIS and assessment of SR/NMA results** | |
| 22. | **\*Synthesis strategy of SR/NMA results**  Describe how you will synthesize the results of included SR/NMA. Importantly, you must be clear on whether you will extract the results from the reports, or if you plan to conduct some calculations. Indicate the software you plan to use for data analysis. |
|  | All meta-analytic calculations for our primary analysis will be performed using the metaumbrella and metaConvert R package. Secondary analyses (on NMAs) will be reconducted only if some methodological decisions differ between our protocol and what original authors did. We will apply the same data analysis strategy as the original authors.  As a sensitivity analysis, we will replicate our primary analysis, but removing studies at high risk of outcome measurement bias |
| 23. | **\*Data analysis strategy** |
|  | Describe all calculations you plan to perform (or results you plan to extract). Be exhaustive in strategy you will use (fixed- vs random-effects model; small-study effects test; excess for statistical significance bias test; heterogeneity indicator). |
|  | We will use a random-effects model with REML estimator for the continuous outcomes, and with a Paule-Mandel estimator for dichotomous outcomes. Egger’s test will be used for assessing the presence of small-study effects. |
| 24. | **\*Assessment of the credibility of the evidence**  State how the quality/credibility of evidence will be assessed. You must be clear on whether you will employ a subjective or objective approach. |
|  | The credibility of the evidence will be assessed using an algorithmic application of the GRADE framework for the main analysis, and using CINeMA for the secondary analyses. The exact CINeMA criteria will be used. The following application of the GRADE criteria will be used:   |  |  | | --- | --- | | *Risk of bias* | * **Two downgrades:** ≥75% of participants included in high-risk studies. * **One downgrade:** 50% to 75% of participants included in high-risk studies. | | *Heterogeneity* | * **Two downgrades:** substantial discrepancy between the 95% CI and 95% PI (e.g., bounds of the 95% CI and 95% PI not of the same sign and in different equivalence ranges). * **One downgrade:** small/moderate discrepancy between the 95% CI and 95% PI (e.g., bounds of the 95% CI and 95% PI of the same sign, but in different equivalence ranges).  Equivalence ranges: * SMD = [-0.10; 0.10] * OR/RR = [0.8; 1.25]   When the 95% PI is not estimable, we will rely on the I² statistic and number of studies with results in the opposite direction to the pooled effect size:   * **Two downgrades:** I² ≥ 50% and ≥10% of studies with results in the opposite direction * **One downgrade:** I² ≥ 30% and ≥10% of studies with results in the opposite direction | | *Indirectness* | * **One downgrade:** heterogeneous mean age of participants, or more than 25% of participants with unknown types of control groups. | | *Imprecision* | * **Two downgrades:** the 95% CI of the pooled effect size includes both null (SMD = 0; RR/OR = 1) and large (SMD >= 0.80; OR/RR >= 5) effects and the meta-analysis does not have the sample size required to detect small effects [eSMD = 0.20] with 80% statistical power. * **Two downgrades:** the meta-analysis does not have the sample size required to detect moderate effects [eSMD = 0.50] with 80% statistical power * **One downgrade:** the 95% CI of the pooled effect size included both null and large effects; or the meta-analysis did not have the sample size required to detect small effects [eSMD = 0.20] with 80% statistical power. | | *Publication bias* | * **One downgrade:** p-value at the Egger’s test was < .10, or more than 50% of participants included in trials with high reporting bias | |