This protocol is written in according to the Preferred Reporting Items for Systematic review and Meta-Analysis protocols (PRISMA-P) (1), the items of A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2) (2), and the guidance notes for registering a systematic review on human studies in the International Prospective Register of Systematic Reviews (PROSPERO) (3).

1. Title

1a: Identification

Effects of Whole-System based interventions with two or more Anthroposophic Medicinal Products: protocol for a systematic review.

2a: Update

The systematic review can be regarded as a second update of the section on “system evaluation of anthroposophic medicine” of a previous Health Technology Assessment Report (4), first update (5).

2. Registration

This systematic review will be registered in PROSPERO.

3. Authors

3a: Contact information

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3b: Contributions

MJ will write the study protocol, support HJH and EB in screening search results by first excluding non-AMP studies found in the systematic literature search, contact authors for unpublished or ongoing studies, evaluate the quality of clinical studies, extract the data from the selected studies and enter data into the database, discuss outcome data and write the scientific manuscript. HJH will co-write the study protocol, screen the

search results for inclusion, analyze and discuss outcome data and co-write the scientific manuscript. EB will co-write the study protocol, screen the search results for inclusion, analyze and discuss outcome data and co-write the scientific manuscript. HvW will evaluate the quality of clinical studies, discuss outcome data and comment on the scientific manuscript. AG will perform searches in non-publicly available databases and provide a list of publications for screening, contact authors for unpublished or on-going studies, extract the data from the selected studies and enter data into the database, discuss outcome data and comment on the scientific manuscript. AB and JÖ will perform searches in public available databases and registers and provide a list of publications for screening, count and exclude duplicates, discuss outcome data and comment on the scientific manuscript. GSK will co-write the study protocol, analyze and discuss outcome data and co-write the scientific manuscript. All authors will approve the final protocol and scientific manuscript.

4. Amendments

The protocol does not represent an amendment of a previously completed or published protocol.

5. Support

5a: Sources

The systematic review is performed on the initiative of the European Scientific Cooperative on Anthroposophic Medicinal Products (ESCAMP, Freiburg, Germany), a non-profit, independent, international cooperative of researchers and experts in the field of AMPs.

5b: Sponsor

This systematic review is funded by grants from Vidarstiftelsen (Järna, Sweden) and the Iona Stichting (Amsterdam, The Netherlands).

5c: Role of the sponsor

Vidarstiftelsen and Iona Stichting are not involved in any aspect of the systematic review, such as the design of the protocol and the collection and analyses of data. Furthermore, the sponsors will have no influence on the interpretation or publication of the study results.

5d: Conflicts of Interest

In the past five years, ESCAMP has received unrestricted (i.e. not dedicated to a specific research project) grants from Wala Heilmittel GmbH and Weleda AG, manufacturers of Anthroposophic Medicinal Products. The relation between ESCAMP and commercial sponsors is regulated in a Conflict of Interest Policy document; these sponsors will have no influence on design, conduct or publication of this systematic review.

6. Rationale

Anthroposophic Medicine (AM) is an integrative whole medical system, founded in Central Europe in the early 1920s. AM therapy aims to stimulate patients' salutogenetic, self-healing capacities (6) and involves specific medicinal products (AMPs) as well as non-medication therapy modalities such as art therapy, rhythmical massage therapy, and eurythmy therapy.

AMPs are manufactured from substances of botanical, mineral and zoological origin (6, 7). The three essential defining features of AMPs are (ESCAMP, 2016):

- conception and development in accordance with the anthroposophic knowledge of man and nature,
- manufacturing by procedures that are:
    - either specifically anthroposophic
    - or common to those of homeopathic medicinal products,
- intended use according to the principles of AM.

AMPs are prescribed by medical doctors practicing in primary, secondary and tertiary care, including inpatient hospitals in Germany, Switzerland, Italy and the USA (6, 8). AMPs are prescribed for the whole range of acute and chronic diseases, with a focus on children's diseases, family medicine, and particularly chronic diseases necessitating long-time complex treatments (6).

AMP therapy is often individualized, involving several AMPs for one indication, simultaneously or in different phases of the course of the disease, and sometimes also AM non-medication therapy. As a result, for patients with the same diagnosis, the individualization often leads to several different therapy options.

Because of the use in all areas of medicine and the individualization, a very large number of AMPs are necessary in order to cover all therapy options. This is a major challenge for research into AMP therapy (6): The traditional, "single product approach" to effect documentation is not feasible, as there is not enough budget and capacity to conduct individual clinical studies for each AMP and therapy option.

However, there is also a different approach, in which the primary assessment of effects takes place on the level of therapy systems such as psychotherapy, surgery, physiotherapy or even drug therapy, while the evaluation of system components comes as a secondary step (9, 10). This systematic review will focus on the effectiveness of AMP therapy within the whole system of AM, whereby non-AM therapies as co-interventions will not be excluded. AMP therapy will include AMP subgroups and combinations of different AMPs, but exclude interventions with one single AMP. This will be referred to as “whole-system based AMP interventions with two or more AMPs”. Such a whole-system based assessment seems to be feasible and appropriate for the evaluation of AMP therapy (11, 12). A strength of system-based evaluations is their high external validity and practice relevance, with clinically relevant settings and a range of patients, therapy administration and outcomes (4).
The two largest evaluations of effectiveness of AMPs on a system level, together including more than 2700 patients are the Anthroposophic Medicine Outcomes Study (AMOS) (13) and the International Integrative Primary Care Outcomes Study (IIPCOS-Anthroposophy) (14). The AMOS study was an observational cohort study of German outpatients treated for mental, musculoskeletal, respiratory, and other chronic conditions. Following AM treatment (AMPs, art therapy, rhythmical massage, eurythmy therapy, physician-provided counseling), substantial and sustained improvements of disease symptoms and quality of life were observed (13), also in patients who received only AMP therapy (15). The IIPCOS study was conducted in four European countries and the United States and compared primary care patients who were treated by medical doctors offering AM integrative or conventional treatment for acute respiratory and ear infections. Compared to conventional therapy, AM treatment, mainly with AMPs, was associated with much lower use of antibiotics and antipyretics as well as quicker recovery, fewer adverse reactions, and greater therapy satisfaction (14).
These studies illustrate the potential for evaluation of the effectiveness of AMP therapy on a system level.

7. Objectives

The aim of this systematic review is to investigate the effectiveness of whole-system based interventions with two or more AMPs.

The Participants, Interventions, Comparators and Outcomes (PICO) are defined as:
Participants: Any type of patients with any type of existing symptom or disease/ disorder(s).
Interventions:

- any intervention including two or more AMPs,
- the AMPs are administered/prescribed in line with the rationale of AM treatment
- further intervention components (e.g. other, non-medication AM therapy) are allowed

Ongoing adjunctive therapies (e.g. conventional treatment) are allowed.
Comparators: Any type of control/comparison or none.
Outcomes: Any clinical outcome or patient-reported outcome.

Review questions
To this end, the proposed systematic review aims to answer the following questions:
1. For which clinical outcomes and or patient-reported outcomes can effectiveness of whole-system AMP interventions be demonstrated via meta-analysis?
2. What is the number (percentage) of studies and outcomes that demonstrate plausibility of positive effects for whole-system AMP interventions on Levels 1, 2 and 3, respectively?
3. What is the range of effect sizes for pre-post studies and controlled studies on whole-system AMP interventions?
4. How does study quality impact the effectiveness of whole-system AMP interventions (questions 1 & 2)?
5. How does study size impact the effectiveness of whole-system AMP interventions (questions 1 & 2)?
6. How does the use of concomitant AM and non-AM therapy impact the effectiveness of whole-system AMP interventions (questions 1 & 2)?
7. Which clinical outcomes and which patient-reported outcomes have been reported for whole-system AMP interventions?
8. To what extent does the body of included studies cover the range of AMP therapy in clinical practice?
9. Which indications (ICD-10 diagnoses) are reported for whole-system AMP interventions?

8. Eligibility criteria

8a: Study designs

In order to answer the research questions, multiple types of study designs will be included in the systematic review (16). Studies included will be randomized controlled trials, controlled (non-randomized) clinical trials, controlled before-after studies, prospective and retrospective comparative clinical studies, non-controlled prospective and retrospective observational studies, cohort studies with before-after design and

case series involving five or more cases (17), provided that they have included and documented these five or more patients allowing for a summative assessment of the cases. Reviews and studies published as master or bachelor theses and unpublished studies for which data are available, will also be included. Studies excluded in the systematic review are case reports, physician experiential reports, cross-sectional studies, qualitative studies, animal and pre-clinical studies, pharmacokinetic or pharmacodynamic trials as well as studies with less than five patients and data from studies that are only available or published in abstract format.

8b: Participants

Any type of patient of all age groups, that is treated for any type of existing symptom or disease/ disorder(s).

8c: Interventions

Whole system based interventions with two or more AMPs.

AMPs are defined according to their development, manufacture and use (18).

They are:

- Conception and development in accordance with the anthroposophic knowledge of man and nature,
- Manufacturing by procedures that are:
    - either specifically anthroposophic
    - or common to those of homoeopathic medicinal products,
- Intended use according to the principles of AM.

Interventions can include any AMP for which the name is clearly described and identifiable, with active ingredients of the AMP that are prepared according to the APC (7) and that is used for treatment of existing symptoms or disorder(s). A whole-system based AMP intervention is defined as an intervention with AMPs, where the AMPs are administered/prescribed in line with the rationale of AM treatment and further intervention components (e.g. other, non-medication AM therapy) are allowed, as well as ongoing adjunctive therapies (e.g. conventional treatment). An intervention with two or more AMPs corresponds to levels 2-5 in Table 1, below. A common feature of these interventions is that effects cannot be attributed to a single AMP. The application of two or more AMPs in the investigated study cohort does not have to be in the same patient or at the same time during the study intervention. Studies which investigate only one AMP (levels 6-8 in table 1) are excluded from this review; they will be assessed elsewhere.

Intervention		Level	Description
I	AM	1	AMPs AND/OR Non-AM therapy modalities
II	**AMPs**	**2**	**Any AMPs**
III	**AMP subgroups**	**3**	**AMPs with identical type of starting material or manufacturing procedures**
		4	**AMPs with similar starting materials and manufacturing procedures**
		5	**AMPs with identical starting material but different manufacturing procedures**
		6	AMPs with identical manufacturer and starting material, but with different dosage forms
IV	Specific AMPs	7	Specific AMP (including different concentrations)
		8	Specific concentration of an AMP

Table 1 Classification of AM and AMP interventions. Interventions on Levels 2-5 are included in this systematic review

8d: Comparators

Studies with any type of control or none, such as placebo, conventional medical treatment, standard care, other active therapy, waiting-list, baseline control, before-after.

8e: Outcomes

Studies will be included in which at least one clinical outcome is described. Outcomes will be extracted in all data forms (e.g. dichotomous, continuous) and from all types of measurement (validated and non-validated scales). Studies that only investigate the safety of AMPs or laboratory parameters that are clearly not related to the improvement of a clinical conditions, symptom or disease and similar, without clinical outcomes, will be excluded.

8f: Timing

There will be no restriction with respect to the length of follow-up of outcomes.

8g: Settings

There will be no restrictions by type of setting.

8h: Language

Studies reported in the Danish, Dutch, English, French, German, Italian, Norwegian, Portuguese, Spanish and Swedish languages will be included. A list of possibly relevant publication of studies in other languages will be provided as an appendix, provided that the abstract of these articles is available in any of the above-mentioned languages.

9. Information sources

Literature search strategies will be developed using medical subject headings (MeSH) and text words related to intervention with AMPs. Searches will be performed in the following databases: AMED, Anthromed Library, Anthromedic.org, Biosis Preview, CAMbase, CINAHL, Cochrane Library (Cochrane Database of Systematic Reviews), EMBASE, LIVIVO, PsychInfo, Pubmed, Researchgate, The NHS Economic Evaluation Database (active up to March 2015), SweMed+, Web of Science. The electronic database search will be supplemented by searching for trial protocols through UK Clinical Trials Gateway (data pooled from ISRCTN and ClinicalTrials.gov), and the WHO trial search portal for studies worldwide. PROSPERO will be searched for ongoing or recently completed systematic reviews. The following databases of guidelines and HTA reports will be searched: www.ahrq.gov, www.leitlinien.de, www.akdae.de, and http://www.inahta.org/hta-tools-resources/database/. The Open-Grey database, PQDT Open database, and the medically-focused deep web search engine Mednar will be used to search doctoral and master theses. To ensure literature saturation, reference lists of included studies or relevant reviews identified through the search will be scanned. Databases of authors and other ESCAMP members will be searched to make sure that all relevant studies will be captured. Furthermore, AMP experts will be identified from a variety of sources (the International Research Advisory Board of the Medical Section at the Goetheanum, manufacturers of AMPs, representatives of AM professional societies and patient groups, AM hospitals, authors of important scientific publications on AM medicine, research institutions conducting research on AM) and asked to provide information about unpublished study reports pertinent to the review. A bibliography of the included articles will be circulated to the ESCAMP members for a final check in order that no other possible eligible studies have been missed.

10. Search strategy

Since over a thousand different AMPs are used in AM, due to lack of research capacity and funding, not all of these can be searched for individually because of their large number. Therefore, names (and parts thereof) of the most common AMPs are included in the search of the databases. The names of AMPs refer in most instances to plants or minerals that are also used in phytotherapy or homeopathy. Database searches using these names therefore will result in a large number of false positive hits, i.e. references referring to studies on homeopathic or herbal preparations. For this reason, specific search terms will be added that relate to anthroposophy, AMP manufacturers and AMP manufacturing procedures which specifically indicate AMPs. The MeSH search strategy will be adapted, using keywords for the electronic databases according to their specific subject headings or structure.

No study design, date or language limits will be imposed on the search, although only studies in languages mentioned under point 8h will be included. The specific search strategies in public databases will be performed by a Health Sciences Librarian with expertise in systematic review searching. A researcher with expertise in AM literature searching will perform the specific search strategies in non-public databases.

The systematic review team will develop the MeSH term search strategy, including the following terms:

Anthroposophy OR anthroposoph* OR Rudolf Steiner OR Waldorf OR Weleda OR Wala OR Helixor OR Abnoba OR Iscador

AND/OR

Study OR Trial OR Evaluat* OR Random* OR Investig* OR Cohort OR Kohort OR Outcome OR Review OR Uebersicht OR Ueberblick OR Metaanalys* OR Meta Analys*

AND/OR

Arzneimittel OR Medicines OR Medication OR Medicinal product* OR Doron* OR Infludo OR Nausyn OR Cardiodoron OR Combudoron OR Hepatodoron OR Choleodoron OR Digestodoron OR Dermatodoron OR Pneumodoron OR Erysidoron OR Kephalodoron OR Biodoron OR Ferrum Quar* OR Menodoron OR Pertudoron OR Echinadoron OR Neurodoron OR Biodor OR Onopordon OR Bidor or Plantago OR Venadoron OR Bolus Eucalypti Comp. OR comp. OR Gencydo OR Mistletoe OR

Viscum OR Iscador OR Iscar OR Iscucin OR Isorel OR Visorel OR Sorel OR Passiflora OR Carum carvi OR Narben OR Planta tota OR planta tota OR Rh OR Radix OR radice OR metallicum praeparatum OR cultum OR culta OR fructibus, OR Fructus OR Gl OR cum OR Digestio OR aa OR Decoctum OR Flos OR Essenz OR Stannum OR ex herba OR ex animale OR Oleum OR Öl OR semine OR foliis OR Eisen OR Floribus OR Globuli velati OR summitatibus OR Summitates

11. Study records

11a: Data management

Literature search results (including abstracts) will be imported into the reference program EndNote in order to facilitate collaboration among reviewers during the study selection process. The systematic review team will develop and test screening questions for assessments based on the inclusion and exclusion criteria. Prior to the formal screening process, the screening questions will be piloted and refined.

11b: Selection process

A single data management file will be produced of all references identified through the search process. Duplicates will be removed from this file. Remaining references will first undergo a process of screening by one review author to exclude all non-AMP studies. Further screening of inclusion and exclusion criteria will be performed by two review authors independently. They will screen subsequently the titles, abstracts and full texts of the searched studies, perform study selection and record their decisions on a standardized eligibility form. Disagreement between the two reviewers will be discussed and solved, and in case of no consensus among the two reviewers, decided by the review team. Additional information from study authors will be sought where necessary to resolve questions about eligibility. Reasons for excluding trials will be documented in each stage of the screening process. Neither of the review authors will be blind to the journal titles, study authors or institutions.

11c: Data collection process

Two review authors will read the articles and independently extract the data that will be entered in duplicate using a standard and piloted extraction form. Any disagreement between the reviewers will be discussed and solved, and in case of no consensus among the two reviewers, will be resolved by discussion among the review team. To ensure consistency across reviewers, a pilot test will be conducted before starting the review. Data abstracted will include general study information, methodology, intervention details, and all reported patient-important outcomes and experiences.

Study authors will be contacted to resolve any uncertainties with respect to eligibility criteria.

12. Data items

For each study report, the following data items will be extracted:

1. General study information: citation (author(s)/ year), publication status, declaration of interest, and funding sources.
2. Study characteristics: objective, study design (e.g. interventional vs. observational, randomized vs. non-randomized controlled, prospective vs. retrospective), population (numbers and age), comparison(s) (placebo, treatment as usual, waiting list, other), indication (ICD-10 diagnosis chapters, diagnosis blocks, three-digit diagnoses), setting, time frame for follow-up.
3. Intervention characteristics: type(s) of AMP treatment, dose, frequency, route and duration of administration, individualized treatment or protocolled treatment, delayed prescription. Any further components of the intervention (AM nonmedication treatment, non-AM treatment)
4. All adjunctive therapies (ongoing at recruitment or used during AMP intervention or during follow-up).
5. Outcome data & grading of conclusion (positive association or no positive association, significant or not significant, clinically relevant or not, event rates (response, recovery etc.), percent reduction of symptoms, effect size (standardized mean difference with 95% confidence intervals and P values)): any clinical outcome such as symptom relief, health-care use, quality of life, symptom duration, re-consultations or other patient-reported outcome.
6. Causal arguments from case-study methodology in favor of a relationship between intervention and observed effect: fast effect, large effect, causal gestalt correspondence (19).

For identifying types of AMP treatment in each study, a classification of AMP groups and individual AMPs will be used (See Table 1, levels 2-5).

If the reported data are insufficient or unambiguous, review authors will contact the corresponding author via email or telephone to request additional information or clarification. The potential impact of missing data on the finding will be reported in the discussion section of the scientific paper.

13. Outcomes and prioritisation

13a: Primary outcomes

Primary outcome is change in any clinical outcome from studies where data can be pooled through meta-analysis. If meta-analysis is not possible, the primary outcome is the plausibility of positive effects (Level 0, 1, 2 and 3; see Table 2) for whole system AMP interventions, in the whole sample of studies and in subgroups according to study design, clinical domains, study quality, studies with AMPs only and studies with AMPs and concomitant AM and non-AM therapy. Plausibility of positive effects is assessed for each study on a numeric rating scale from Level 0 (lowest plausibility) to Level 3 (highest plausibility), according to criteria developed in conjunction with the ESCAMP Monograph Project (20) (Table 2).

13b Secondary outcomes

Secondary outcome will be all (other) reported clinical outcomes and other outcomes relevant for patient care such as changes in symptoms, symptom duration, healthcare use, drug use, quality of life, disease scores, remission time, re-consultations, laboratory test, physical activity tests, occurrence of complications, and/ or time to discharge, avoidance of conventional medication with high incidence of ADRs and toxicity risks, less ADRs with comparable clinical outcomes and patient experiences (including satisfaction) after AMP intervention. Other outcomes are indications for AMP therapy (ICD-10 diagnosis chapters, diagnosis blocks, three-digit diagnoses) and number of AMPs and AMP Groups (grouped according to levels 2-5 in Table 1, dependent on findings) used by ≥ 5 patients in all included studies.

14. Appraisal of study quality and clinical relevance

The methodological quality of the included studies will be assessed with the critical appraisal tools from the Joanna Briggs Institute (21). In addition, quality criteria as developed by Kienle et al. (5) will be assessed for each study insofar as they are not already included in the critical appraisal tools from the Joanna Briggs Institute (4). The quality criteria of Kienle et al. have been developed in accordance with the guidelines of the ‘Complementary Medicine Evaluation Programme’ (22) and international guidelines for HTA reporting (23, 24). Two review authors will conduct study quality assessment independently and decide which studies are of low quality and which studies of higher quality. Discrepancies between the reviewers’ quality assessments will be discussed and resolved, and in case of no consensus among the two reviewers, will be resolved by discussion among the review team. A table will be generated with descriptive statistics for each quality item among all studies with this design.

Using a 7-item appraisal tool for practice relevance of clinical studies developed by Kienle et al. (5), the practice relevance will be assessed independently by two medical doctors who have been regular prescribers of AMPs in their work for at least 5 years.

15. Data synthesis

Evidence for review question 1 will be obtained through meta-analyses. It is anticipated that there will be limited scope for meta-analysis because of the range of different outcomes and study design across the studies that will be included. However, if studies have used the same type of study design, comparator, indication (diagnosis chapters and/or diagnosis blocks and/or three-digit diagnoses), and with the same outcome measure, data will be pooled using a random-effects model analysis with standardized mean differences for continuous outcomes and risk ratios for binary outcomes, and calculation of 95% confidence intervals and two sided P values for each outcome. Heterogeneity between the studies in effect measures will be assessed using both the chi-squared test and the I-squared statistic. An I-squared value greater than 50% will be considered indicative of substantial heterogeneity.

In order to answer review question 2, a set of algorithms for each main type of study design will be used to classify the plausibility of positive effects of each study on a scale from 0 to 3, where 0 is the lowest level of plausibility and 3 the highest level (see Table 2). Subsequently, the number of studies in each category will be organized according to study design, clinical domains, and intervention (AMPs only vs. AMPs plus other therapy components).

Table 2. Assessment criteria for plausibility of positive effects

<table>
<tr><th colspan="2">Plausibility criteria*</th></tr>
<tr><td colspan="2">Level 0
Criteria for Level 1 are not fulfilled</td></tr>
<tr><td colspan="2">Level 1
1. Indication sufficiently described for identification
AND
2. Therapy administration: minimally required dose and concentration required for the AMP therapy to work
AND
3. The AMP therapy is associated with clinical benefits for at least one clinical outcome</td></tr>
<tr><td>Pre-post studies</td><td>Studies with a concurrent control group**</td></tr>
<tr><td>Level 2
1-3
AND:
4. The study outcome cannot be explained by attrition bias
AND</td><td>Level 2
1-3
AND:
4. The study outcome cannot be explained by attrition bias
OR</td></tr>
</table>

5. The study outcome cannot be explained by adjunctive therapies	5. The study outcome cannot be explained by adjunctive therapies
Level 3 1-5 and: 6. Combined bias suppression (25) OR “TCR series” = studies/case series with judgment of effectiveness in each patient according to cognition based medicine (19)	**Level 3** 1-3 AND: 4. The study outcome cannot be explained by attrition bias **AND** 5. The study outcome cannot be explained by adjunctive therapies

*The plausibility criteria are currently under development and may be subject to change. **Studies with a concurrent control group that have an additional design or analysis feature in order to minimize bias, such as randomization, adjustment for confounders, stratification, matched pairs, propensity score matching or penalty design.

Evidence for review question 3 will be calculated and categorized according to Cohen’s d effect size (small: 020-0.49, moderate: 0.50-0.79, large: ≥0.80) (26) and/or changes in symptom scores: symptoms gone (100% symptom reduction), greatly improved (75-99 % symptom reduction), improved (50-74% symptom reduction), moderately improved (25-49% symptom reduction), slightly improved (1-24% symptom reduction), not improved (0% symptom reduction), worse (increase of symptoms). For pre-post studies, pre-post effect sizes will be calculated using the standard deviation of the baseline score variable (27). When necessary and where possible, study authors will be contacted to provide missing data for effect size calculations. Binary outcomes will be classified as event rates.

For review question 4 and 5, sensitivity analyses will be performed in order to assess the impact of study size (small studies < 50 patients, large studies ≥ 50 patients) and study quality (low versus higher quality).

The possible impact of adjunctive therapies (review question 6) is assessed in the procedure for plausibility of effect Level 2 (see Table 2).

For review questions 7-9, outcome data will be described in a narrative style, and/or reported in extraction tables, and where appropriate in the text. Data on socio-demographics, indications for AMP therapy (ICD diagnoses), number of AMPs used by at least 5 patients in the respective studies and methodological study quality will be described and tabulated.

Meta-biases

The potential impact of non-publication bias and outcome reporting bias will be discussed in the discussion section of the scientific paper. In case that trial protocols were published, study protocols will be compared with published data in order to identify possible outcome reporting bias.

16. Confidence in the body of evidence

The systematic review will describe the effectiveness of whole-system based interventions with two or more AMP. Conclusions will be drawn in terms of effectiveness of specific clinical outcomes or number (%) of studies with positive plausibility effects for whole-system AMP interventions or range of effect sizes. Furthermore, the systematic review will give a clear overview of the number of studies included, the type of studies included, total number of patients, total number of AMPs used for a number of different indications, study quality and range of clinical outcomes.

17. Dissemination of results

Results will be published in a scientific peer-reviewed journal and may be presented at scientific conferences.

18. References

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