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Comparing the effectiveness, safety, and tolerability of interventions for depressive symptoms in people with multiple sclerosis: a systematic review and network meta-analysis protocol

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SCHOLARONE™
Manuscripts

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3 **Title: Comparing the effectiveness, safety, and tolerability of interventions for depressive**
4 **symptoms in people with multiple sclerosis: a systematic review and network meta-**
5 **analysis protocol**
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10
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1
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3 **Word count: 3221**
4

5 **ABSTRACT**
6

7 **Background**
8

9
10 Comorbid depression is prevalent in people with multiple sclerosis (MS). Depression is
11 commonly untreated or undertreated and there is a need for effective and safe interventions.
12
13 Guidelines for depression management in people with MS recommend psychological and
14
15 pharmaceutical interventions, however current research suggests other interventions such as
16
17 exercise could also be effective. The comparative efficacy and safety between intervention
18
19 modalities have not been established in the literature.
20
21
22

23 **Objective:**
24

25
26 To outline a protocol for a systematic review and network meta-analysis to compare efficacy
27
28 and safety of psychological, pharmaceutical, physical, and magnetic stimulation interventions
29
30 for depression in people with MS.
31
32

33 **Methods and analysis:**
34

35 We will search seven key databases using a search strategy developed for this protocol with
36
37 search terms revolving around three concepts: MS, depression, and randomised controlled
38
39 trials. Included trials will be randomised controlled trials with depression as the primary
40
41 outcome, only outcome, or secondary outcome with *a priori* power calculation with a
42
43 population of people with MS using an aforementioned intervention type will be included.
44
45 Screening, data extraction, and risk of bias assessment (using the Risk of Bias 2 tool) will be
46
47 conducted by two independent reviewers. We will generate descriptive statistics and provide a
48
49 narrative synthesis of the included trials. We will use a frequentist multivariate random effects
50
51 model in a network meta-analysis where efficacy will be measured using a standardised mean
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1
2
3 difference and safety using an odds ratio. If possible, we will provide summary measures
4 including a geometry of the network, surface under the cumulative ranking curve, and a
5 league table. Sub-group analysis will be performed if possible, using pre-planned variables.
6
7

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9
10 **Ethics and dissemination:**

11
12 Ethical approval is not necessary for this type of study. Results of the systematic review and
13 network meta-analysis will be published in a peer reviewed journal.
14

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17 **Review registration:**

18
19 PROSPERO registration number CRD42020209803.
20
21

22
23
24 **STRENGTHS AND LIMITATIONS OF THIS STUDY:**

- 25
26 • This will be the first systematic review and network meta-analysis to identify the
27 comparative efficacy, safety, and tolerability of interventions for depression in people with
28 MS.
29
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31
32
33 • Eligibility criteria include randomised controlled trials which are limited to depression as the
34 primary outcome, only outcome, or secondary outcome with a power analysis.
35
36
37
38 • The review will include multiple intervention types which are used in both clinical and
39 research settings.
40
41
42
43 • To meet the transitivity assumption, trials including participants with treatment
44 resistant/refractory depression must be excluded.
45

46
47 **KEYWORDS:** multiple sclerosis, depression, network meta-analysis, systematic review,
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51 **ARTICLE TYPE:** protocol
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INTRODUCTION:

Multiple Sclerosis (MS) is a chronic, immune mediated and neurodegenerative disease characterised by the formation of destructive lesions predominantly involving myelinated axons within in the central nervous system ¹. There are a broad range of symptoms attributed to the multifocal lesions distinctive of MS including depression, pain, fatigue, impaired gait, incontinence, impaired vision, and spasticity ². Depression can be particularly burdensome, and affects up to 50% of people with MS ³. Depressive symptoms in people with MS are reported to impact adherence to disease modifying therapies ⁴, increase pain sensitivity ², and reduce participation in work and poor health related quality of life ⁵. Major depressive disorder (MDD), the most commonly diagnosed depressive disorder, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is defined as experiencing a minimum of five symptoms including depressed mood or lack of pleasure, feelings of worthlessness/guilt, fatigue, appetite or weight changes, psychomotor agitation, diminished concentration, feelings of worthlessness/guilt, suicidality and sleep difficulties within a period of two-weeks ⁶. Depressive symptoms which do not meet the definition of MDD are even more prevalent in people with MS, and commonly still require treatment ⁷. Furthermore, people with MS who have moderate-to-severe depressive symptoms have been reportedly underdiagnosed and undertreated ^{8,9}. The aetiology of depression and depressive symptoms in people with MS is not yet fully understood but ¹⁰ but due to the multitude of effects, safe and effective interventions are required.

Guidelines for treating depression in people with MS suggest that a combination of psychological and pharmaceutical interventions is the most effective two-pronged therapy ¹¹

1
2
3 12. Further, the American Association of Neurology review to inform guidelines in 2014¹³
4
5 point out the scarcity of trials to treat depression in people with MS, and therefore a lack of
6
7 strong evidence. Following this pivotal review¹³ a number of studies have sought to address
8
9 the dearth in literature. Some interventions, such as mindfulness-based interventions¹⁴ and
10
11 Pilates¹⁵ have not been included in these guidelines. Further, recent systematic reviews
12
13 reported that exercise^{16 17} and mindfulness-based interventions¹⁸, compared to waitlist/usual
14
15 care, have a moderate effect at reducing depressive symptoms in people with MS. However,
16
17 it is unclear how these interventions compare in terms of efficacy and safety. Network meta-
18
19 analysis enables the comparison of multiple interventions by combining the direct and indirect
20
21 evidence without the need for several analyses¹⁹. Synthesising the evidence in this manner
22
23 will enable a comprehensive understanding of how interventions compare, which should
24
25 greatly enhance evidence-based decision making for people with MS and their clinicians on
26
27 how best to manage depressive symptoms.
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34
35 This article outlines the protocol for a systematic review and network meta-analysis to
36
37 compare the effectiveness and safety of intervention modalities, or combination of modalities,
38
39 in reducing depressive symptoms in adults with MS. This review is the first stage of a larger
40
41 project that aims to provide guidance for public health researchers on the design and analysis
42
43 of network meta-analysis studies in MS.
44
45
46

47 **METHODS**

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51 This systematic review protocol is registered with The International Prospective Register of
52
53 Systematic Reviews (PROSPERO) (CRD42020209803) and adheres to the Preferred
54
55 Reporting Items for Systematic Reviews and Meta-Analyses extension for Network Meta-
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3 Analysis (PRISMA NMA) statement ²⁰, see supplementary file 1 for checklist.
4
5

6 7 **Eligibility criteria**

8 9 **Participants**

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11
12
13 Adults (aged 18 years or older) of any gender who have been diagnosed with any type of MS.
14
15

16 17 **Interventions**

18
19
20 We will include interventions that aim to alleviate depressive symptoms in people with MS,
21
22 including:
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24

25
26
27 *Psychological interventions* will be delivered with the intention of treating depressive
28
29 symptoms, informed by psychological theories or principle(s) and a) implemented by a
30
31 psychiatrist/psychologist or other mental health clinician or b) manualized, with content
32
33 developed by a mental health clinician or researcher, e.g. online/app or web-based
34
35 intervention.
36
37

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39
40 *Pharmaceutical interventions* will be delivered with the intention involve the use of
41
42 medication or drugs for the intention of treating depressive symptoms at a therapeutic dose
43
44 according to the manufacturer guidelines (if available).
45
46

47
48
49 *Physical interventions* including physiotherapy and physical activity (any bodily movement
50
51 that results in energy expenditure) including exercise, aimed at treating depressive symptoms.
52

53 Subtypes of physical activity will be included.
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2
3 *Electromagnetic stimulations* involve the use of targeted electromagnetic stimulation to
4 stimulate areas of the brain to reduce depressive symptoms. Subtypes include transcranial
5 magnetic stimulation, and transcranial direct current stimulation.
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10
11 Combinations of the above-mentioned intervention modalities will be included and will form
12 new categories. Any interventions that are specific to people with treatment resistant
13 depression/refractory depression will not be included (e.g. electroconvulsive therapy). This is
14 because participants who have treatment resistant depression will have previously participated
15 in first step methods such as cognitive behavioural therapy and to satisfy the transitivity
16 assumption ¹⁹ (i.e., a participant who does not have treatment resistant depression would not
17 be eligible to be randomised to an intervention such as electroconvulsive therapy).
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29 Grouping of interventions will depend on the eligible trials. The four broad categories will be
30 split into smaller sub-categories, e.g. psychological interventions could have a sub-category of
31 mindfulness-based interventions, similarly pharmaceutical interventions could have a sub-
32 category of serotonin reuptake inhibitors.
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40 Comparator

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42
43 We will consider the following comparators: any intervention modality included in the above
44 list, placebo, wait-list control, treatment as usual, or no treatment. Classification of comparator
45 groups will depend on the type of comparator the author of the RCT has employed. Common
46 types of comparators can include, but not limited to, placebo, wait-list control, treatment as
47 usual, and no treatment control. These comparator groups do not have similar methodology
48 and can influence participant outcome in altering ways. Therefore, for this protocol and
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1
2
3 subsequent systematic review and network meta-analysis, we will adopt the recommended
4 framework for classification of comparator groups ²¹. The groups will be (1) minimal
5 treatment control, active control, or similar; (2) wait-list control, treatment as usual, or no
6 treatment; and (3) pill placebo.
7
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12

13 Outcome

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15
16
17 We will include studies which specified that depressive symptoms were the primary (or only)
18 outcome, or as a secondary outcome where an a-priori power calculation was provided. The
19 severity of depressive symptoms must have been measured by a validated self-report
20 questionnaire or by clinician interview. Although depression and depressive symptoms is
21 measured and defined differently across studies ²², we have chosen to accept all types of
22 standardised measures or clinical interviews. To assess the acute efficacy of the intervention,
23 depressive symptoms must be measured within two weeks of completion of the intervention.
24
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33 We will also assess the long-term efficacy of the intervention using studies that have
34 measured depressive symptoms at approximately six months post-intervention (within 4-8
35 months). Any studies that have measured just one of the aforementioned time points will still
36 be eligible for inclusion.
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44 Safety and tolerability outcomes will include:

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47
48 - Frequency of serious adverse events (SAEs) defined as an untoward occurrence of a medical
49 event that is fatal, life-threatening, requires hospitalization or prolonging of existing
50 hospitalization and/or persistent disability ²³⁻²⁶.
- 51
52
53
54 - Frequency of adverse events (AEs) defined as the occurrence of an undesirable event
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3 occurring during the study duration even if the event was not considered to be related to the
4
5 intervention ²³⁻²⁶.

6
7
8 - Tolerability of the intervention will be assessed as the frequency of participants who
9
10 discontinue the study and/or have reduced compliance due to SAE or AEs ^{23 27}.

11
12
13
14 The events will be measured as dichotomous outcomes during the intervention period and
15
16 SAE's and AE's might be combined in analysis if they are rare outcomes of the studies.

17 18 19 20 Types of Studies

21
22
23
24 We will include randomised controlled trials, including multi-arm randomised trials. Quasi-
25
26 randomised, cluster and cross-over trials will not be included.

27 28 29 30 Search strategy

31
32
33 We will search the following seven databases: EMBASE, Ovid (Medline), Cochrane
34
35 CENTRAL, APA PsycInfo, Web of Science, CINAHL and PEDro. The search strategy was
36
37 developed in conjunction with a medical librarian at the University of Melbourne, Australia,
38
39 as well as a clinical physiotherapist (YL) who works with people with MS, and a clinical
40
41 psychologist (AM). The search terms relate to three main concepts of MS, depression, and
42
43 randomised controlled trials. Search strategies for all databases are listed in supplementary file
44
45
46
47 2. Databases will be searched from inception to present. We will also search the reference lists
48
49 of relevant systematic reviews to identify any randomised trials that might have been missed
50
51 in the database search. Trials will be limited to those published in English.

52 53 54 55 56 Study selection

1
2
3 Results from the search strategy will be uploaded to Endnote ²⁸ where duplicates will be
4 removed. The remaining citations will be uploaded into the software management system
5
6 Covidence ²⁹ where any additional duplicates will be removed. Covidence will then be used
7
8 for title and abstract screening and full text screening by at least two independent reviewers
9
10 with any conflicts resolved by a third reviewer.
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15

16 **Data Extraction**

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18
19
20 Data will be extracted using a data extraction tool developed for this review using Excel
21
22 software by at least two independent reviewers, with conflicts resolved by a third reviewer. If
23
24 data was missing from the published article the corresponding author will be contacted. We
25
26 will not look at other sources of citations such as grey literature, clinical trial registries, or
27
28 protocol papers. The extracted data will relate to the following categories:
29
30
31

- 32
33 - Study characteristics: first author's last name, year of publication, year of baseline
34
35 recruitment, method of recruitment, method of randomisation, inclusion criteria (e.g. a
36
37 baseline level of depression cut off for inclusion into study).
38
39
- 40 - Sample demographics: sample size, number of participants randomised, baseline
41
42 characteristics such as diagnosis of MS, age (years), sex, years since diagnosis of MS, level of
43
44 disability, and disability tool.
45
46
- 47 - Intervention and comparator characteristics: type, frequency of intervention/treatment,
48
49 duration of intervention/treatment, and dose of intervention/treatment.
50
51
- 52 - Efficacy outcome data: type of outcome measurement scale, mean and standard deviation of
53
54 depressive symptom score at baseline, post-intervention, and at six months post-intervention
55
56 (if available).
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3 - Safety and tolerability data: type and number of all SAEs and AE, number of participants
4 that discontinue due to an SAE or AE or for other reasons during the intervention reported for
5 each trial arm (if time-point data is available, this information will be extracted).
6
7

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9
10 - Data relating to the risk of bias assessment: randomisation process, allocation concealment,
11 deviations from intended treatment, baseline characteristics differences, missing outcome
12 data, appropriateness of outcome measurement, potential influence in outcome assessment,
13 and selectively reporting results.
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21 **Risk of bias assessment**

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23
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25 We will use the Risk of Bias 2 tool (RoB 2) to assess the risk of bias for each study that meets
26 the eligibility criteria³⁰. This tool evaluates the risk of bias in five key domains:
27 randomisation process, deviations from intended interventions, missing outcome data,
28 measurement of the outcome, and selection of the reported result. The RoB 2 tool provides an
29 overall assessment of the risk of bias in the study using three categories: low risk, some
30 concerns or high risk of bias. At least two independent reviewers will assess the risk of bias in
31 each study with any conflicts between judgements resolved by a third reviewer. In this
32 systematic review and network meta-analysis there will be an inherent difference in the
33 overall risk of bias between studies due to the type of intervention. Blinding of the participants
34 to the assigned intervention is difficult in some study designs and interventions. For example,
35 participants in a two-arm randomised trial that compared exercise to wait-list control will be
36 aware of the treatment arm they were allocated in the randomisation process, whereas
37 participants in a pharmaceutical intervention which compared an anti-depressant to placebo
38 have reasonable doubt as to which intervention they were allocated. Blinding of the outcome
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3 assessors can also be difficult in these trials as depressive symptoms are typically measured
4 using self-reported tools. Despite this inherent difference we have chosen not to deviate from
5 the protocol of the RoB 2 tool or alter the tool in any way.
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9

10 11 **Data synthesis**

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14
15 All analyses will be conducted using Stata version 16.1 using the network package ³¹.
16
17

18 19 Characteristics of the included studies

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22
23 We will generate descriptive statistics for the sample populations to understand the
24 demographics of the review participants across all eligible trials. These descriptive statistics
25 will describe key clinical and methodological characteristics such as age, sex, type of MS, and
26 type of intervention modality.
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32 33 Outcome data

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37 For this network meta-analysis, we will have two primary and two secondary outcomes.
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39

40 41 *Primary outcome:*

- 42
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44
45 (1) efficacy of intervention(s) at post-intervention using standardised mean difference ³²,
46
47 and
48
49 (2) safety of interventions (SAEs, AEs and tolerability) using pooled odds ratios at post-
50
51 intervention.
52
53

54 55 *Secondary outcome:*

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2
3 (1) efficacy of intervention(s) at post-intervention using standardised mean difference at
4 six months post-intervention (between four and eight months)
5

6
7 (2) safety of interventions (SAEs, AEs and tolerability) using pooled odds ratios at six
8 months post-intervention (between four and eight months)
9
10
11

12 13 14 15 Geometry of the network

16
17
18 We will generate a network diagram, separately for efficacy and safety, to visualise the
19 network of intervention modalities. The nodes (or intervention modalities) will represent the
20 total number of studies in that group; the larger the size of the node the larger the sample size.
21
22 The edges of the lines connecting each node will represent the precision of the evidence, i.e.,
23 the thicker the line the more precise evidence. Figure 1 shows an example of the possible
24 network structure with the major intervention modalities included.
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34 **<insert figure 1 here>**
35
36

37 38 Pairwise Meta-analysis

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41 For each major category of intervention modality (i.e. psychological, pharmaceutical,
42 physical, electromagnetic stimulation therapies or combination) that is informed by 10 or
43 more trials in the category we will fit a random effects pairwise meta-analysis. The random
44 effects model will assume that the underlying intervention effects across the studies are
45 similar but not identical allowing an estimation of the heterogeneity in the model³³. This will
46 be performed for both the efficacy outcome, using the SMD, and the safety outcome, using
47 odds ratios. Effect sizes will be presented with their corresponding 95% confidence intervals.
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3 Heterogeneity will be estimated using the I^2 statistic giving a percentage of variation across
4 the studies due to heterogeneity ³⁴.
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8 9 Assessment of transitivity in the network 10

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13 The transitivity assumption, which underpins the method of a network meta-analysis, states
14 that any participant in one trial could be equally randomised to any other trial in the network
15 ¹⁹. Participant characteristics (for example, age, sex, type of MS, level of disability, and years
16 since diagnosis of MS) might cause the transitivity assumption to be violated ¹⁹. For example,
17 if participants in a trial comparing pharmacological interventions were eligible for recruitment
18 if they had severe mobility disability and they would never be eligible for a trial comparing
19 two physical activity interventions then we would conclude that the transitivity assumption
20 has potentially been violated. To assess transitivity of the network the inclusion criteria for
21 participants recruited into each trial will be assessed. If the transitivity assumption is thought
22 to be violated, we will undertake narrative synthesis of the data (described below) and
23 possibly pair wise meta-analyses (described above). If we find no reason to suggest that
24 violation of the transitivity assumption, we will synthesise the available evidence using
25 network meta-analysis techniques. We will fit a random effects network meta-analysis model
26 in a frequentist framework and assume a common heterogeneity parameter across the eligible
27 trials. The random effects model assumes that the variation between studies could be a result
28 of heterogeneity and not from sampling variation ^{19 31}.
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51 Summary Statistics 52

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55 We will present the summary SMDs or ORs for all pairwise comparisons in a league table ³⁵
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1
2
3 36. We will use a predictive interval plot to show the grouped intervention modality SMD or
4 OR in a future trial 35. We will then obtain a hierarchy of the intervention modalities using the
5
6 surface under the cumulative ranking curve (SUCRA). SUCRA uses probabilities to
7
8 determine which intervention modality is most likely to be the most effective at reducing
9
10 depressive symptoms in people with MS. A probability of 1 (or 100%) is indicative of the
11
12 stated intervention modality being the most effective intervention modality, conversely, a
13
14 probability of 0 (or 0%) is indicative of the stated intervention modality being the least
15
16 effective 36.
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23 Assessment of inconsistency

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25
26
27 Consistency is a measure of the agreement between direct evidence and indirect evidence. If
28
29 inconsistency occurs in a network it may suggest that there is significant heterogeneity and
30
31 that the transitivity assumption could be violated 19 33. Using the network meta-analysis
32
33 package in Stata a consistency and inconsistency model can be separately applied to assess
34
35 whether the direct and indirect evidence are in agreement for each outcome. These models can
36
37 provide information to help ascertain if the direct and indirect evidence are in statistical
38
39 agreement 37. If there is evidence of inconsistency in the network, we will use a local method
40
41 with the side-splitting approach, a technique that divides the evidence within a node and
42
43 analyses it separately to identify if the evidence agrees with the network, to identify if there is
44
45 a specific modality of interventions that contribute to inconsistency in the network 31 37. This
46
47 will enable us to further investigate the possible sources of inconsistency 38.
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53 Sub-group analysis

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3 We will conduct separate sub-group analyses for the efficacy and the safety outcome if there
4 is substantial heterogeneity and the data allows this.
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8
9 For the efficacy outcome we will assess whether the following characteristics might explain
10 any of the observed heterogeneity in the model using a sub-group analysis:
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13

- 14
15 - Year of baseline recruitment; to determine if treatments have become more effective over
16 time.
17
- 18
19 - Severity of depression at baseline (i.e., studies that recruited based on level of depression vs.
20 studies that did not); to identify whether interventions are efficacious when a level of
21 depressive symptoms is present.
22
23
- 24
25 - Comparison of self-reported outcome measures vs clinical assessment; to determine if there
26 is a difference in the efficacy of the treatment due to the measurement of the outcome.
27
28
- 29
30 - Level of disability at enrolment (e.g., as measured by Patient determined disease steps,
31 Expanded Disability Disease Scale: categorized in mild, moderate severe); to determine if
32 level of disability is associated with the efficacy of the intervention.
33
34
- 35
36 - Whether the intervention was conducted in a dose according to guidelines that exist for that
37 type of interventions (e.g., exercise guidelines for people with MS); to determine if a
38 minimum dose is associated with the efficacy of the intervention.
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45 For the safety and tolerability outcome we will assess whether year of baseline recruitment
46 and level of disability at enrolment might explain any of the observed heterogeneity.
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52 Assessment of small study effects
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56 We will use the comparison-adjusted³⁵ and contour-enhanced³⁹ funnel plots to investigate
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3 whether results in imprecise trials differ from those in more precise trials. Network meta-
4 regression models will be used to investigate associations between study sample size and
5 effect size ⁴⁰.
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9

10 11 Narrative synthesis

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14
15 If we are unable to conduct a NMA or meta-analyses we plan to conduct a narrative synthesis
16 to assess which interventions reported the outcomes of interest and if there were any patterns
17 relating to specific interventions, or gaps in the literature.
18
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22

23 24 **ETHICS AND DISSEMINATION**

25
26
27 Ethical approval is not needed for a systematic review and network meta-analysis as this study
28 will use aggregated data from already published RCT's. The dissemination of the results of
29 the systematic review and network meta-analysis will include publishing in a peer reviewed
30 journals to apprise MS researchers and clinicians, and people with MS. The results of the
31 systematic review and network meta-analysis have the potential to inform future treatment
32 guidelines for depression in people with MS. Further, the review may highlight any gaps in
33 the literature and provide recommendations for the conduct and reporting of future
34 randomised controlled trials.
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46 47 **AUTHORS CONTRIBUTIONS**

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51 AK and CM conceived the study. AK, CM, JL, SC, YL, AGK and AM contributed to the
52 study design. JL drafted the manuscript and AK, CM, SC, YL edited the manuscript. All
53 authors read and approved the final manuscript.
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CONFLICT OF INTEREST

The authors declare no conflict of interest.

PATIENT AND PUBLIC INVOLVEMENT

Neither patients nor the public were involved in the design, conduct, reporting, or dissemination plans of the research in this article.

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28 **FIGURE LEGEND:**

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32 Figure 1: The possible network structure for the major categories of interventions. Comparator
33 group(s) may be split into multiple nodes as outlined in the comparator group section.
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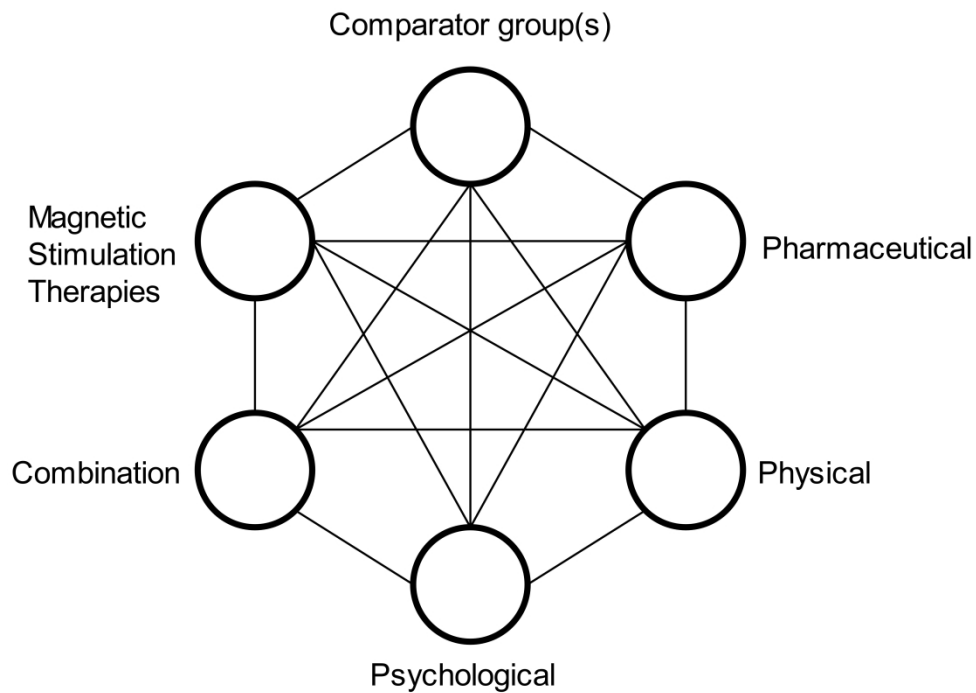


Figure 1: The possible network structure for the major categories of interventions. Comparator group(s) may be split into multiple nodes as outlined in the comparator group section.

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SUPPLEMENTARY FILE 1:

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Table 1: PRISMA-NMA guidelines checklist.

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PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	6-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	Supplementary file 2

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1			including any limits used, such that it could be repeated.	
2	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9-10
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7	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10-11
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10	Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10-11
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13	Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	13
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20	Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	11-12
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25	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	15
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31	Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i> 	12-17
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40	Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	15
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44	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	16-17
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47	Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network; and</i> • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i> 	15-16
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1	Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	NA
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3	Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	NA
4				
5	Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	NA
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11	Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
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14	Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	NA
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17	Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	NA
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22	Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	NA
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30	Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	NA
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36	Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	NA
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38	Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>).	NA
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DISCUSSION

Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	NA
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	NA
FUNDING			18
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this

SUPPLEMENTARY FILE 2:**Complete database search strategy**

Table 1: search strategy for databases EMBASE, APA PsycInfo, Ovid MEDLINE, Cochrane CENTRAL.

	Search terms
1	multiple sclerosis.ti,ab.
2	exp multiple sclerosis/
3	1 or 2
4	exp depression/
5	(depress* or mood disorder or despair or misery or unhappiness or dysthymia or dysphor* or seasonal affective disorder or affective disorder or sadness or loss of pleasure).ti,ab.
6	4 or 5
7	exp randomized controlled trial/
8	("random* control* trial*" or RCT or "random-allocation*" or "random allocation*" or "double-blind*" or "double blind*" or "single-blind*" or "single blind*" or mask* or random* or "control* stud*" or "control* clinical trial*" or "comparative stud*").ti,ab.
9	7 or 8
10	3 AND 6 AND 9

Table 2: search strategy for databases CINAHL and Web of Science.

	Search Term
1	“multiple sclerosis”
2	depress* or “mood disorder*” or despair or misery or unhappiness or dysthymia or dysphor* or “seasonal affective disorder” or “affective disorder” or sadness or “loss of pleasure”
3	("random* control* trial*" or RCT or "random-allocation*" or "random allocation*" or "double-blind*" or "double blind*" or "single-blind*" or "single blind*" or mask* or random* or "control* stud*" or "control* clinical trial*" or "comparative stud*")
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Table 3: search strategy for PEDro database.

	Search line
1	“multiple sclerosis” and depress*

For peer review only

BMJ Open

Comparing the effectiveness, safety, and tolerability of interventions for depressive symptoms in people with multiple sclerosis: a systematic review and network meta-analysis protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-055796.R1
Article Type:	Protocol
Date Submitted by the Author:	04-Mar-2022
Complete List of Authors:	Lyons, Julia; The University of Melbourne School of Population and Global Health, Disability and Health Unit Campese, Stephanie; The University of Melbourne School of Population and Global Health, Disability and Health Unit Learmonth, Yvonne ; Murdoch University, Discipline of Exercise Science & Centre for Molecular Medicine and Innovative Therapeutics, Health Futures Institute; Perron Institute for Neurological and Translational Science Metse, Alexandra; University of Newcastle, School of Psychology; University of the Sunshine Coast, School of Health and Behavioural Sciences Kermode, Allan; Perron Institute for Neurological and Translational Science; Murdoch University, Centre for Molecular Medicine and Innovative Therapeutics, Health Futures Institute Karahalios, Amalia; The University of Melbourne School of Population and Global Health, Centre for Epidemiology and Biostatistics Marck, C; The University of Melbourne School of Population and Global Health, Disability and Health Unit
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Neurology
Keywords:	Multiple sclerosis < NEUROLOGY, MENTAL HEALTH, Depression & mood disorders < PSYCHIATRY, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts

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3 1 **Title: Comparing the effectiveness, safety, and tolerability of interventions for depressive**
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5 2 **symptoms in people with multiple sclerosis: a systematic review and network meta-**
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7 3 **analysis protocol**
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11 4 Julia Lyons ^a, Stephanie Campese ^a, Yvonne C Learmonth ^{b,c,d}, Alexandra Metse ^{e, f}, Allan G.
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13 5 Kermode ^{c,d}, Amalia Karahalios ^{g*}, Claudia H Marck ^{a*}
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3 28 **ABSTRACT**
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5 29 **Background**
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8 30 Comorbid depression is prevalent in people with multiple sclerosis (MS). Depression is
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10 31 commonly untreated or undertreated and there is a need for effective and safe interventions.
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12 32 Current guidelines recommend psychological and pharmaceutical interventions for the
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14 33 management of depression in people with MS. However, current research suggests other
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16 34 interventions, such as exercise, could also be effective. The comparative efficacy and safety of
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18 35 intervention modalities have not been established in the literature.
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24 37 We plan to conduct a systematic review and network meta-analysis to compare efficacy and
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26 38 safety of psychological, pharmaceutical, physical, and magnetic stimulation interventions for
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28 39 depression in people with MS.
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33 41 **Methods:**
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35 42 We will search seven key databases with search terms revolving around three concepts: MS,
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37 43 depression, and randomised controlled trials. Included studies will be randomised controlled
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39 44 trials, where the participants are people with MS people that are randomised to receive one of
40
41 45 the aforementioned intervention types. For a trial to be included, depression or depressive
42
43 46 symptoms will be the primary outcome, only outcome, or secondary outcome with an *a priori*
44
45 47 power calculation. Screening of the citations and full text articles, data extraction, and risk of
46
47 48 bias assessment (using the Risk of Bias 2 tool - RoB 2) will be conducted by two independent
48
49 49 reviewers. We plan to pool the trials using pairwise and network meta-analysis. For the
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53 50 pairwise meta-analyses, we will fit a random effects model. For the network meta-analysis, we
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3 51 will fit a frequentist multivariate random effects model. For the pairwise and network meta-
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5 52 analysis models, efficacy will be measured using a standardised mean difference, and safety
6
7 53 using an odds ratio. If possible, we will provide summary measures including forest plots, a
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10 54 geometry of the network, surface under the cumulative ranking curve, and a league table.
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12 55 Subgroup analysis will be performed if possible, using pre-planned variables.
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15 56 **Review registration:**

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17 57 PROSPERO registration number CRD42020209803.
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21 59 **STRENGTHS AND LIMITATIONS OF THIS STUDY:**

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23
24 60 • This will be the first systematic review and network meta-analysis to quantify the
25
26 61 comparative efficacy, safety, and tolerability of interventions for depression in people with
27
28 62 MS.
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31 63 • Eligibility criteria include randomised controlled trials which are limited to depression as the
32
33 64 primary outcome, only outcome, or secondary outcome with a power analysis.
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35 65 • The review will aim to simultaneously compare intervention types that are used in both
36
37 66 clinical and research settings.
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39
40 67 • To meet the transitivity assumption, trials that include participants with treatment
41
42 68 resistant/refractory depression will be excluded.
43
44

45 69 **KEYWORDS:** multiple sclerosis, depression or depressive symptoms, network meta-
46
47 70 analysis, systematic review.
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51 71 **ARTICLE TYPE:** protocol
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73 INTRODUCTION:

74 Multiple Sclerosis (MS) is a chronic, immune mediated and neurodegenerative disease
75 characterised by the formation of destructive lesions predominantly involving myelinated
76 axons within the central nervous system ¹. There are a broad range of symptoms attributed to
77 the multifocal lesions distinctive of MS including depression and depressive symptoms, pain,
78 fatigue, impaired gait, incontinence, impaired vision, and spasticity ². Depression can be
79 particularly burdensome, and affects up to 50% of people with MS ³. Depressive symptoms in
80 people with MS are reported to impact adherence to disease modifying therapies ⁴, and
81 increase pain sensitivity ². Further, reduced participation in work and depressive symptoms
82 are associated with poor health related quality of life ⁵ in people with MS. Major depressive
83 disorder is the most commonly diagnosed depressive disorder ⁶. It is defined as experiencing a
84 minimum of five of the following symptoms within a two-week period: depressed mood or
85 lack of pleasure, feelings of worthlessness/guilt, fatigue, appetite or weight changes,
86 psychomotor agitation, diminished concentration, feelings of worthlessness/guilt, suicidality
87 and sleep difficulties ⁶. Depressive symptoms which do not meet the definition of major
88 depressive disorder are even more prevalent in people with MS, and commonly require
89 treatment ⁷. Furthermore, people with MS who have moderate-to-severe depressive symptoms
90 have been reportedly underdiagnosed and undertreated ^{5,8}. The aetiology of depression and
91 depressive symptoms in people with MS is not yet fully understood ⁹ but due to the multitude
92 of effects, safe and effective interventions are required.

93 Guidelines for treating depression in people with MS suggest that a combination of
94 psychological and pharmaceutical interventions is the most effective therapy in reducing

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3 95 levels of depressive symptoms^{10 11}. Specifically, these guidelines recommend
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5 96 pharmacotherapies such as antidepressants, psychological treatments such as cognitive
6
7 97 behavioural therapy, and, where applicable and safe, exercise-based interventions¹¹.
8
9
10 98 However, some interventions, including third wave cognitive and behavioural (psychological)
11
12 99 interventions that emphasise the role of mindfulness¹² and specific types of exercise such as
13
14 100 Pilates¹³, have not been included in these guidelines. The American Association of
15
16 101 Neurology review to inform guidelines¹⁴ noted the scarcity of trials to treat depression in
17
18 102 people with MS and therefore a lack of strong evidence. Following this review¹⁴, several
19
20 103 studies have sought to address the treatment of depressive symptoms in MS. Evidence from
21
22 104 systematic reviews reported that exercise^{15 16} and mindfulness-based interventions¹⁷ when
23
24 105 compared to waitlist/usual care have a moderate effect at reducing depressive symptoms in
25
26 106 people with MS. However, it is unclear how these interventions compare in terms of efficacy
27
28 107 and safety.
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34 108 Network meta-analysis enables the comparison of multiple interventions by simultaneously
35
36 109 combining direct and indirect evidence¹⁸. Synthesising the evidence in this manner will
37
38 110 enable a comprehensive understanding of how interventions compare (in terms of efficacy and
39
40 111 safety), which should greatly enhance evidence-based decision making for people with MS
41
42 112 and their clinicians on how best to manage depressive symptoms. The major assumption
43
44 113 underpinning network meta-analysis methods ensures that we can compare two interventions
45
46 114 via a third (common) intervention and is referred to as transitivity. Transitivity requires that
47
48 115 the trials included in the network meta-analysis are considered to be ‘jointly randomisable’,
49
50 116 that the common intervention (comparator) from the different trials is similar enough to be
51
52 117 combined, and that the characteristics associated with the effect of the intervention are similar
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3 118 across the included trials^{19 20}.
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6
7 119 This article outlines the protocol for a systematic review and network meta-analysis to
8
9 120 compare the effectiveness and safety of intervention modalities, or combination of modalities,
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11 121 in reducing depressive symptoms in adults with MS. This review is the first stage of a larger
12
13 122 project that aims to provide guidance for public health researchers on the design and analysis
14
15 123 of systematic reviews with network meta-analysis and future trials in MS.
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19 20 124 **METHODS** 21 22

23
24 125 This systematic review protocol is registered with The International Prospective Register of
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26 126 Systematic Reviews (PROSPERO) (CRD42020209803) and adheres to the Preferred
27
28 127 Reporting Items for Systematic Reviews and Meta-Analyses extension for Network Meta-
29
30 128 Analysis (PRISMA NMA) statement ²¹, see supplementary file 1 for checklist.
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32
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34 129 **Patient and public involvement** 35 36 37

38 130 Neither patients nor the public were involved in the design, conduct, or reporting of the
39
40 131 research in this article.
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42
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44 132 **Eligibility criteria** 45 46

47 133 **Participants** 48 49

50 134 Adults (aged 18 years or older) of any gender who have been diagnosed with any type of MS.
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53

54 135 **Interventions** 55 56 57 58 59 60

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2
3 136 We will include interventions that aim to alleviate depressive symptoms in people with MS,
4
5 137 including:

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8
9 138 *Psychological interventions* delivered with the intention of treating depressive symptoms,
10
11 139 informed by psychological theories or principle(s) and a) implemented by a
12
13 140 psychiatrist/psychologist or other mental health clinician or b) manualized, with content
14
15 141 developed by a mental health clinician or researcher, e.g., online/app or web-based
16
17 142 intervention.

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21
22 143 *Pharmaceutical interventions* that involve the use of medication or drugs for the intention of
23
24 144 treating depressive symptoms at a therapeutic dose according to the manufacturer guidelines
25
26 145 (if available).

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29
30
31 146 *Physical interventions* including physiotherapy and physical activity (any bodily movement
32
33 147 that results in energy expenditure) including exercise, aimed at treating depressive symptoms.
34
35 148 Subtypes of physical activity will be included.

36
37
38
39 149 *Electromagnetic stimulations* involve the use of targeted electromagnetic stimulation to
40
41 150 stimulate areas of the brain to reduce depressive symptoms. Subtypes include transcranial
42
43 151 magnetic stimulation, and transcranial direct current stimulation.

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46
47 152 Combinations of the above-mentioned intervention modalities will be included and will form
48
49 153 new categories. Any interventions that are specific to people with treatment resistant
50
51 154 depression/refractory depression will not be included (e.g., electroconvulsive therapy). These
52
53 155 treatments will be excluded because they will compromise the transitivity assumption (i.e.,
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3 156 that all interventions are considered to be ‘jointly randomisable’). Treatments for people with
4
5 157 treatment resistant depression would not be considered to meet this assumption because they
6
7
8 158 are not considered first line treatments for people with MS¹⁸.
9

10
11 159 Grouping of interventions will depend on the eligible trials. The four broad categories will be
12
13
14 160 split into smaller sub-categories, e.g., psychological interventions could have a sub-category
15
16 161 of mindfulness-based interventions, similarly pharmaceutical interventions could have a sub-
17
18 162 category of serotonin reuptake inhibitors.
19

20 21 22 163 Comparator 23

24
25
26 164 We will consider the following comparators: any intervention modality included in the above
27
28 165 list, placebo, wait-list control, treatment as usual, or no treatment. Classification of comparator
29
30 166 groups will depend on the type of comparator used in the original randomised trial. Common
31
32 167 types of comparators can include, but are not limited to, placebo, wait-list control, treatment
33
34 168 as usual, and no treatment control. These comparator groups do not have similar methodology
35
36
37 169 and can influence participant outcome in altering ways. Therefore, for this protocol and
38
39 170 subsequent systematic review and network meta-analysis, we will adopt the recommended
40
41 171 framework for classification of comparator groups²². The groups will be (1) minimal
42
43 172 treatment control, active control, or similar; (2) wait-list control, treatment as usual, or no
44
45 173 treatment; and (3) pill placebo.
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50 51 174 Outcome 52

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54 175 We will include trials that specified that depressive symptoms were the primary (or only)
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3 176 outcome, or as a secondary outcome where an *a-priori* power calculation was provided. The
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5 177 severity of depressive symptoms must have been measured by a validated self-report
6
7
8 178 questionnaire or by clinician interview. Although depression and depressive symptoms are
9
10 179 likely to be measured and defined differently across trials ²³, we have chosen to accept all
11
12 180 types of standardised measures or clinical interviews. To assess the acute efficacy of the
13
14
15 181 intervention, depressive symptoms must be measured within two weeks of completion of the
16
17 182 intervention. We will also assess the long-term efficacy of the intervention using trials that
18
19 183 have measured depressive symptoms at approximately six months post-intervention (within 4-
20
21 184 8 months). To measure long term efficacy and safety of interventions for reducing depressive
22
23
24 185 symptoms we will also extract the relevant data that is measured 12 or more months post-
25
26 186 intervention. Any trials that have measured just one of the aforementioned time points will
27
28 187 still be eligible for inclusion.

30
31
32 188 Safety and tolerability outcomes will include:

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34
35
36 189 - Frequency of serious adverse events (SAEs) defined as an untoward occurrence of a medical
37
38 190 event that is fatal, life-threatening, requires hospitalisation or prolonging of existing
39
40
41 191 hospitalisation and/or persistent disability ²⁴⁻²⁷.
- 42
43 192 - Frequency of adverse events (AEs) defined as the occurrence of an undesirable event
44
45 193 occurring during the study duration even if the event was not considered to be related to the
46
47 194 intervention ²⁴⁻²⁷.
- 48
49
50 195 - Tolerability of the intervention will be assessed as the number of participants who
51
52 196 discontinue the study and/or have reduced compliance due to SAE or AEs ^{24 28}.

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56 197 The events will be measured as dichotomous outcomes during the intervention period. We
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3 198 will consider combining the SAE's and AE's if they are rare events in the trials.
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7 199 **Types of Studies**
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10 200 We will include randomised controlled trials, including multi-arm randomised trials. Quasi-
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12 201 randomised, cluster and cross-over trials will not be included.
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17 202 **Search strategy**
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20 203 We will search the following seven databases: EMBASE, Medline, Cochrane CENTRAL,
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22 204 APA PsycInfo, Web of Science, CINAHL and PEDro. Note that EMBASE, Medline,
23
24 205 Cochrane CENTRAL and APA PsycInfo will be searched through the Ovid platform. The
25
26 206 search strategy was developed in conjunction with a medical librarian at the University of
27
28 207 Melbourne, Australia, as well as a clinical physiotherapist (YL) who works with people with
29
30 208 MS, and a clinical psychologist (AM). The search terms relate to three main concepts of MS,
31
32 209 depression, and randomised controlled trials. Search strategies for all databases are listed in
33
34 210 supplementary file 2. All databases were searched from inception to the 11th of July 2020 and
35
36 211 the search will be updated to include articles published up to the 31st of December 2021. We
37
38 212 will also search the reference lists of relevant systematic reviews to identify any randomised
39
40 213 trials that might have been missed in the database search. Trials will be limited to those
41
42 214 published in English.
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50 215 **Study selection**
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53 216 Results from the search strategy will be uploaded to Endnote²⁹ where duplicates will be
54
55 217 removed. The remaining citations will be uploaded into the software management system
56
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1
2
3 218 Covidence³⁰ where any additional duplicates will be removed. Covidence will then be used
4
5 219 for title and abstract screening and full text screening by at least two independent reviewers
6
7
8 220 with any conflicts resolved by a third reviewer.
9

11 221 **Data Extraction**

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14
15 222 Data will be extracted using a data extraction tool developed for this review using Excel
16
17 223 software by at least two independent reviewers, with conflicts resolved by a third reviewer. If
18
19 224 data were missing from the published article the corresponding author will be contacted. We
20
21 225 will not look at other sources of citations such as grey literature, clinical trial registries, or
22
23 226 protocol papers. The extracted data will relate to the following categories:
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25

- 26
27
28 227 - Study characteristics: first author's last name, year of publication, year of baseline
29
30 228 recruitment, method of recruitment, method of randomisation, inclusion criteria (e.g., a
31
32 229 baseline level of depression cut off for inclusion into study).
33
34 230 - Sample demographics: sample size, number of participants randomised, baseline
35
36 231 characteristics such as diagnosis of MS, age (years), sex, years since diagnosis of MS, level of
37
38 232 disability, and disability tool.
39
40 233 - Intervention and comparator characteristics: type, frequency of intervention/treatment,
41
42 234 duration of intervention/treatment, and dose of intervention/treatment. We will use TIDieR for
43
44 235 clear reporting of the characteristics of the interventions and comparators³¹.
45
46
47 236 - Efficacy outcome data: type of outcome measurement scale, mean and standard deviation of
48
49 237 depressive symptom score at baseline, post-intervention, at six months post-intervention, and
50
51 238 at 12 months post-intervention (if available).
52
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54 239 - Safety and tolerability data: type and number of SAEs and AEs, number of participants that
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3 240 discontinue participation due to an SAE or AE or discontinue participation for other reasons
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5 241 during the intervention. Safety and tolerability data will be extracted for each trial arm and
6
7 242 time point where available.

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9
10 243 - Data relating to the risk of bias assessment: randomisation process, allocation concealment,
11
12 244 deviations from intended treatment, baseline characteristics differences, missing outcome
13
14 245 data, appropriateness of outcome measurement, potential influence in outcome assessment,
15
16 246 and selectively reporting results.
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19 247

20 21 248 **Risk of bias assessment**

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24
25 249 We will use the RoB 2 to assess the risk of bias for each study that meets the eligibility criteria
26
27 250 ³². This tool evaluates the risk of bias in five key domains: randomisation process, deviations
28
29 251 from intended interventions, missing outcome data, measurement of the outcome, and
30
31 252 selection of the reported result. The RoB 2 tool provides an overall assessment of the risk of
32
33 253 bias in the study using three categories: low risk, some concerns or high risk of bias. At least
34
35 254 two independent reviewers will assess the risk of bias in each study with any conflicts
36
37 255 between judgements resolved by a third reviewer. In this systematic review and network meta-
38
39 256 analysis there will be an inherent difference in the overall risk of bias between trials due to the
40
41 257 type of intervention. Blinding of the participants to the assigned intervention is difficult in
42
43 258 some study designs and interventions. For example, in a trial that randomised participants to
44
45 259 exercise and wait-list control, participants will be aware of the treatment arm that they were
46
47 260 allocated to. However, in a trial that randomised participants to an anti-depressant and
48
49 261 placebo, participants are unlikely to be aware which treatment they were allocated. As well,
50
51 262 blinding of the outcome assessors can also be difficult in these trials as depressive symptoms
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263 are typically measured using self-reported tools. Despite this inherent difference we have
264 chosen not to deviate from the protocol of the RoB 2 tool or alter the tool in any way.

265 **Data synthesis**

266 Characteristics of the included trials

267 We will generate descriptive statistics for the sample populations to understand the
268 demographics of the review participants across all eligible trials. These descriptive statistics
269 will describe key clinical and methodological characteristics such as age, sex, type of MS, and
270 type of intervention modality.

271 Outcome data

272 We will have two primary and two secondary outcomes.

273 *Primary outcomes:*

- 274 (1) efficacy of the interventions (reduction of depressive symptoms) measured
275 immediately post-intervention and quantified using standardised mean difference³³, and
- 276 (2) safety of the interventions (SAEs, AEs and tolerability) measured immediately post-
277 intervention and quantified using odds ratios.

278 *Secondary outcomes:*

- 279 (1) efficacy of the interventions (reduction of depressive symptoms) measured
280 immediately six months post-intervention (between four and eight months) and quantified

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3 281 using standardised mean differences;
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5 282 (2) safety of the interventions (SAEs, AEs and tolerability) measured six months post
6
7
8 283 intervention (between four and eight months) and quantified using odds ratios;
9

10 284 (3) efficacy of intervention (reduction of depressive symptoms) measured 12 months post-
11
12 285 intervention (12 months or longer) and quantified using standardised mean differences;
13

14 286 (4) safety of interventions (SAEs, AEs and tolerability) measured 12 months post-
15
16
17 287 intervention (12 months or longer) and quantified using odds ratios.
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19 288

20
21 289 Pairwise Meta-analysis
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25 290 First, we will pool the data that compare the same major category of intervention modality
26

27 291 (i.e., psychological, pharmaceutical, physical, electromagnetic stimulation therapies or
28

29 292 combination) to each other or to placebo/usual care by fitting a random effects pairwise meta-
30

31 293 analysis model and using the restricted maximum likelihood estimator to estimate the between
32

33 294 study heterogeneity. The random effects model will assume that the underlying intervention
34

35 295 effects across the trials are similar but not identical allowing an estimation of the
36

37 296 heterogeneity in the model³⁴. This will be performed for both the efficacy outcome, using the
38

39 297 standardised mean difference, and the safety outcome, using odds ratios. Effect sizes will be
40

41 298 presented with their corresponding 95% confidence intervals. Heterogeneity will be estimated
42

43 299 using the I^2 and τ^2 statistics³⁵.
44
45

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48
49 300 Network meta-analysis model
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52
53 301 We will fit a multivariate meta-analysis contrast-based model within a frequentist framework
54

55 302 using the network package in Stata³⁶. We will assume common heterogeneity across the
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1
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3 303 trials.
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7 304 Geometry of the network
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10 305 We will generate a network diagram, separately for efficacy and safety, to visualise the
11
12 306 network of intervention modalities. The nodes (or intervention modalities) will represent the
13
14 307 total number of trials in each treatment group; the larger the size of the node the larger the
15
16 308 sample size. The edges of the lines connecting each node will represent the precision of the
17
18 309 evidence, i.e., the thicker the line the more precise evidence. Figure 1 shows an example of the
19
20 310 possible network structure with the major intervention modalities included.
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25
26 311 **<insert figure 1 here>**
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29

30 312 Assessment of transitivity in the network
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34 313 The transitivity assumption, which underpins the method of a network meta-analysis, requires
35
36 314 that the characteristics associated with the effect of the intervention are similar across the
37
38 315 included trials¹⁸. Participant characteristics (for example, age, sex, type of MS, level of
39
40 316 disability, and years since diagnosis of MS) could indicate violation of the transitivity
41
42 317 assumption¹⁸. To assess this requirement of the transitivity assumption the characteristics of
43
44 318 the participants recruited into each trial will be summarised and compared. If this requirement
45
46 319 of the transitivity assumption is thought to be violated, we will undertake narrative synthesis
47
48 320 of the data (described below) and possibly pair wise meta-analyses (described above). If we
49
50 321 find no reason to suggest that violation of the transitivity assumption, we will synthesise the
51
52 322 available evidence using network meta-analysis techniques. We will fit a random effects
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3 323 network meta-analysis model in a frequentist framework and assume a common heterogeneity
4
5 324 parameter across the eligible trials. The random effects model assumes that the variation
6
7 325 between trials could be a result of heterogeneity and not from sampling variation^{18 36}.

11 326 Summary Statistics and presentation of results

15 327 We will present forest plots that will include pooled estimates from the direct and mixed
16
17 328 intervention effects and league tables with the summary standardised mean differences or
18
19 329 odds ratios for all pairwise comparisons^{37 38}. We will use a predictive interval plot to show the
20
21 330 grouped intervention modality standardised mean differences or odds ratios in a future trial³⁷.
22
23 331 We will then obtain a hierarchy of the intervention modalities using the surface under the
24
25 332 cumulative ranking curve (SUCRA). SUCRA uses probabilities to determine which
26
27 333 intervention modality is most likely to be the most effective at reducing depressive symptoms
28
29 334 in people with MS. A probability of 1 (or 100%) is indicative of the stated intervention
30
31 335 modality being the most effective intervention modality, conversely, a probability of 0 (or 0%)
32
33 336 is indicative of the stated intervention modality being the least effective³⁸.

39 337 Assessment of inconsistency

43 338 Consistency is a measure of the agreement between direct evidence and indirect evidence. If
44
45 339 inconsistency occurs in a network it may suggest that there is significant heterogeneity and
46
47 340 that the transitivity assumption could be violated^{18 34}. Using the network meta-analysis
48
49 341 package in Stata³⁶ a consistency and an inconsistency model can be separately fitted to assess
50
51 342 whether the direct and indirect evidence are in agreement for each outcome. These models can
52
53 343 provide information to help ascertain if the direct and indirect evidence are in statistical

1
2
3 344 agreement³⁹. If there is evidence of inconsistency in the network, we will use the side-
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5 345 splitting approach to identify if there is a specific modality of interventions that contribute to
6
7 346 inconsistency in the network^{36,39}. This will enable us to further investigate the possible
8
9 347 sources of inconsistency⁴⁰.

13 14 348 Subgroup analysis

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16
17 349 We will conduct separate subgroup analyses for the efficacy and the safety outcome if there is
18
19 350 substantial heterogeneity or inconsistency and the data allows this.

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23 351 For the efficacy outcome, we will assess the following subgroups:

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26
27 352 – Year of baseline recruitment; to determine if treatments have become more
28
29 353 effective over time.
- 30
31
32 354 – Severity of depression at baseline (i.e., trials that recruited based on level of
33
34 355 depression vs trials that did not); to determine whether interventions are efficacious
35
36 356 when a level of depressive symptoms is present.
- 37
38
39 357 – Comparison of self-reported outcome measures vs clinical assessment; to
40
41 358 determine if there is a difference in the efficacy of the treatment due to the
42
43 359 measurement of the outcome.
- 44
45
46 360 – Level of disability at enrolment (e.g., as measured by Patient determined disease
47
48 361 steps, Expanded Disability Disease Scale: categorised in mild, moderate or severe
49
50 362 disability); to determine if level of disability is associated with the efficacy of the
51
52 363 intervention.
- 53
54
55 364 – Whether the intervention was conducted in a dose according to guidelines that
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3 365 exist for that type of interventions (e.g., exercise guidelines for people with MS);
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5 366 to determine if a minimum dose is associated with the efficacy of the intervention.
6

7
8 367 For the safety and tolerability outcome we will undertake subgroup analyses by year of
9
10 368 baseline recruitment and level of disability at enrolment.
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14 370 Assessment of small study effects
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18 371 We will use the comparison-adjusted³⁷ and contour-enhanced⁴¹ funnel plots to investigate
19
20 372 whether results in imprecise trials differ from those in more precise trials. Network meta-
21
22 373 regression models will be used to investigate associations between study sample size and
23
24 374 effect size⁴².
25
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28

29 375 Narrative synthesis
30

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32
33 376 If we are unable to conduct a NMA or pairwise meta-analyses we plan to conduct a narrative
34
35 377 synthesis to assess which interventions reported the outcomes of interest and if there were any
36
37 378 patterns relating to specific interventions, or gaps in the literature.
38
39
40

41 379 **ETHICS AND DISSEMINATION**

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44

45 380 Ethical approval is not needed for a systematic review and network meta-analysis as we will
46
47 381 use aggregated data from previously published randomised trials. The dissemination of the
48
49 382 results of the systematic review and network meta-analysis will include publishing in a peer
50
51 383 reviewed journals to apprise MS researchers and clinicians, and people with MS. The results
52
53 384 of the systematic review and network meta-analysis have the potential to inform future
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3 385 treatment guidelines for depression in people with MS. Further, the review may highlight any
4
5 386 gaps in the literature and provide recommendations for the conduct and reporting of future
6
7
8 387 randomised trials.
9

10 11 388 **AUTHORS CONTRIBUTIONS**

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14
15 389 AK and CHM conceived the study. AK, CHM, JL, SC, YL, AGK and AM contributed to the
16
17 390 study design. JL drafted the manuscript and AK, CHM, SC, YL edited the manuscript. All
18
19 391 authors read and approved the final manuscript.
20
21
22

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25
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27
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29
30 395 (ID 20-216).
31
32

33 396 **CONFLICT OF INTEREST**

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36
37 397 The authors declare no conflict of interest.
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39

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37 523 **FIGURE LEGEND:**

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41 524 Figure 1: The possible network structure for the major categories of interventions. Comparator
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43 525 group(s) may be split into multiple nodes as outlined in the comparator group section.
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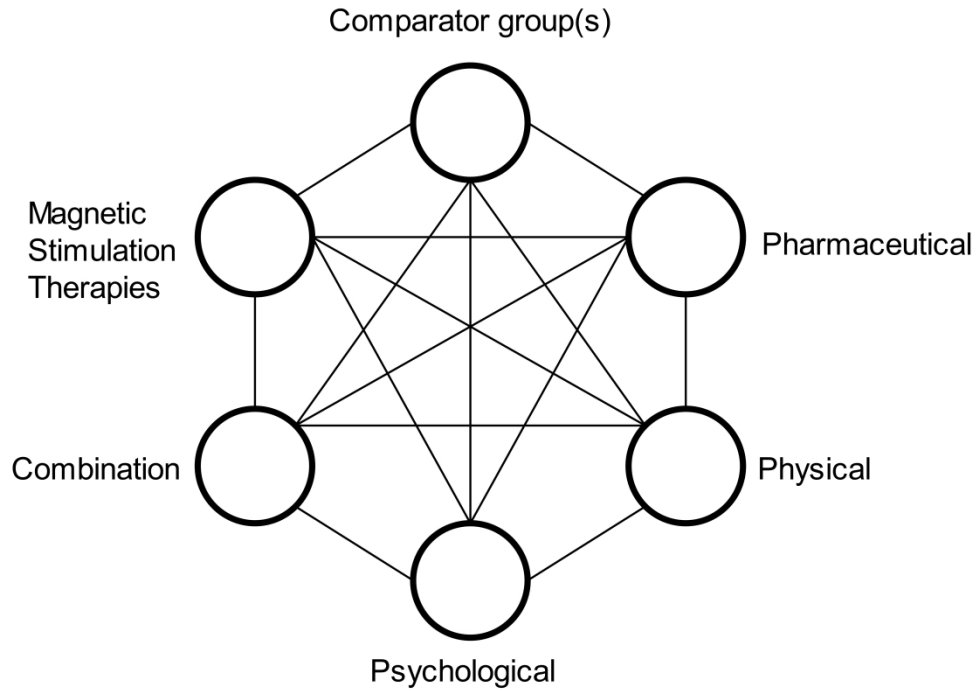


Figure 1: The possible network structure for the major categories of interventions. Comparator group(s) may be split into multiple nodes as outlined in the comparator group section.

2053x1443mm (72 x 72 DPI)

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SUPPLEMENTARY FILE 1:

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Table 1: PRISMA-NMA guidelines checklist.

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PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	6-10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	Supplementary file

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1			including any limits used, such that it could be repeated.	
2	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	10-11
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7	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	11-12
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10	Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11-12
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13	Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	15
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20	Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	12-13
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25	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	16
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31	Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i> 	14-18
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40	Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	15-16
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44	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	18
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47	Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network; and</i> • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i> 	17-18
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1	Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	NA
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3	Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	NA
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5	Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	NA
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11	Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
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14	Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	NA
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17	Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	NA
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22	Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	NA
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31	Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	NA
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36	Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	NA
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38	Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>).	NA
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60**DISCUSSION**

Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	NA
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	NA
FUNDING			19
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this

SUPPLEMENTARY FILE 2:**Complete database search strategy**

Supplementary Table 1: Search strategy for databases EMBASE, APA PsycInfo, MEDLINE, Cochrane CENTRAL, searched through the Ovid platform.

	Search terms
1	multiple sclerosis.ti,ab.
2	exp multiple sclerosis/
3	1 or 2
4	exp depression/
5	(depress* or mood disorder or despair or misery or unhappiness or dysthymia or dysphor* or seasonal affective disorder or affective disorder or sadness or loss of pleasure).ti,ab.
6	4 or 5
7	exp randomized controlled trial/
8	("random* control* trial*" or RCT or "random-allocation*" or "random allocation*" or "double-blind*" or "double blind*" or "single-blind*" or "single blind*" or mask* or random* or "control* stud*" or "control* clinical trial*" or "comparative stud*").ti,ab.
9	7 or 8
10	3 AND 6 AND 9

Supplementary Table 2: Search strategy for databases CINAHL through the Scopus platform*, and Web of Science searched through the Web of Science platform*.

	Search Term
1	“multiple sclerosis”
2	depress* or “mood disorder*” or despair or misery or unhappiness or dysthymia or dysphor* or “seasonal affective disorder” or “affective disorder” or sadness or “loss of pleasure”
3	("random* control* trial*" or RCT or "random-allocation*" or "random allocation*" or "double-blind*" or "double blind*" or "single-blind*" or "single blind*" or mask* or random* or "control* stud*" or "control* clinical trial*" or "comparative stud*")
4	1 AND 2 AND 3

*The search strategy for Scopus platform and Web of Science platform is the same.

Supplementary Table 3: Search strategy for PEDro database.

	Search line
1	“multiple sclerosis” and depress*

For peer review only

BMJ Open

Comparing the effectiveness, safety, and tolerability of interventions for depressive symptoms in people with multiple sclerosis: a systematic review and network meta-analysis protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-055796.R2
Article Type:	Protocol
Date Submitted by the Author:	18-May-2022
Complete List of Authors:	Lyons, Julia; The University of Melbourne School of Population and Global Health, Disability and Health Unit Campese, Stephanie; The University of Melbourne School of Population and Global Health, Disability and Health Unit Learmonth, Yvonne ; Murdoch University, Discipline of Exercise Science & Centre for Molecular Medicine and Innovative Therapeutics, Health Futures Institute; Perron Institute for Neurological and Translational Science Metse, Alexandra; University of Newcastle, School of Psychology; University of the Sunshine Coast, School of Health and Behavioural Sciences Kermode, Allan; Perron Institute for Neurological and Translational Science; Murdoch University, Centre for Molecular Medicine and Innovative Therapeutics, Health Futures Institute Karahalios, Amalia; The University of Melbourne School of Population and Global Health, Centre for Epidemiology and Biostatistics Marck, C; The University of Melbourne School of Population and Global Health, Disability and Health Unit
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Neurology
Keywords:	Multiple sclerosis < NEUROLOGY, MENTAL HEALTH, Depression & mood disorders < PSYCHIATRY, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts

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3 1 **Title: Comparing the effectiveness, safety, and tolerability of interventions for depressive**
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5 2 **symptoms in people with multiple sclerosis: a systematic review and network meta-**
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7 3 **analysis protocol**
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11 4 Julia Lyons ^a, Stephanie Campese ^a, Yvonne C Learmonth ^{b,c,d}, Alexandra Metse ^{e,f}, Allan G.
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13 5 Kermode ^{c,d}, Amalia Karahalios ^{g*}, Claudia H Marck ^{a*}
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28 **ABSTRACT**

29 **Background**

30 Comorbid depression is prevalent in people with multiple sclerosis (MS). Depression is
31 commonly untreated or undertreated, thus, there is a need for effective and safe interventions
32 and current guidelines recommend psychological and pharmaceutical interventions for people
33 with MS. However, research suggests that other interventions, such as exercise, could also be
34 effective. The comparative efficacy and safety of intervention modalities have not been
35 quantified.

36
37 We plan to conduct a systematic review and network meta-analysis to compare efficacy and
38 safety of psychological, pharmaceutical, physical, and magnetic stimulation interventions for
39 depression in people with MS.

40 **Methods and analysis:**

41 We will search EMBASE, Medline, Cochrane CENTRAL, APA PsycInfo, Web of Science,
42 CINAHL and PEDro from inception to 31/12/2021. Search terms will stem from three
43 concepts: MS, depression, and randomised controlled trials. Included studies will be
44 randomised controlled trials, where participants are people with MS randomised to receive
45 one of the aforementioned intervention types, and depression or depressive symptoms is the
46 primary outcome, only outcome, or secondary outcome with an *a priori* power calculation.
47 Screening, data extraction, and risk of bias assessment (using the Risk of Bias 2 tool) will be
48 conducted independently by two reviewers. If possible, we will synthesise the evidence by
49 fitting a frequentist network meta-analysis model with multivariate random effects, or a
50 pairwise random-effects meta-analysis model. For each model, efficacy will be measured

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2
3 51 using a standardised mean difference, and safety using an odds ratio. We plan to provide
4
5 52 summary measures including forest plots, a geometry of the network, surface under the
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7
8 53 cumulative ranking curve, and a league table, and perform subgroup analyses. Otherwise, a
9
10 54 narrative review will be provided.

11
12 55 **Ethics and dissemination:**

13
14
15 56 Ethics is not required for a systematic review and network meta-analysis. Results will be
16
17 57 published in a peer reviewed journal.

18
19 58 **Review registration:**

20
21 59 PROSPERO registration CRD42020209803.
22
23
24 60

25
26 61 **STRENGTHS AND LIMITATIONS OF THIS STUDY:**

- 27
28 62 • Advanced network meta-analysis methods together with sensitivity and subgroup analyses
29
30 63 will comprehensively quantify the comparative efficacy, safety, and tolerability of several
31
32 64 interventions for depression in people with MS.
- 33
34 65 • This systematic review will use a detailed search strategy and pre-specified eligibility
35
36 66 criteria, with all steps of the review process conducted independently by two reviewers.
- 37
38 67 • Eligibility criteria include randomised controlled trials which are limited to depression as the
39
40 68 primary outcome, only outcome, or secondary outcome with a power analysis.
- 41
42 69 • To meet the transitivity assumption, trials that include participants with treatment
43
44 70 resistant/refractory depression will be excluded.

45
46
47 71 **KEYWORDS:** multiple sclerosis, depression or depressive symptoms, network meta-
48
49 72 analysis, systematic review.
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51

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55 73 **ARTICLE TYPE:** protocol
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74 INTRODUCTION:

75 Multiple Sclerosis (MS) is a chronic, immune mediated and neurodegenerative disease
76 characterised by the formation of destructive lesions predominantly involving myelinated
77 axons within the central nervous system ¹. There are a broad range of symptoms attributed to
78 the multifocal lesions distinctive of MS including depression and depressive symptoms, pain,
79 fatigue, impaired gait, incontinence, impaired vision, and spasticity ². Depression can be
80 particularly burdensome, and affects up to 50% of people with MS ³. Depressive symptoms in
81 people with MS are reported to impact adherence to disease modifying therapies ⁴, and
82 increase pain sensitivity ². Further, reduced participation in work and depressive symptoms
83 are associated with poor health related quality of life ⁵ in people with MS. Major depressive
84 disorder is the most commonly diagnosed depressive disorder ⁶. It is defined as experiencing a
85 minimum of five of the following symptoms within a two-week period: depressed mood or
86 lack of pleasure, feelings of worthlessness/guilt, fatigue, appetite or weight changes,
87 psychomotor agitation, diminished concentration, feelings of worthlessness/guilt, suicidality
88 and sleep difficulties ⁶. Depressive symptoms which do not meet the definition of major
89 depressive disorder are even more prevalent in people with MS, and commonly require
90 treatment ⁷. Furthermore, people with MS who have moderate-to-severe depressive symptoms
91 have been reportedly underdiagnosed and undertreated ^{5,8}. The aetiology of depression and
92 depressive symptoms in people with MS is not yet fully understood ⁹ but due to the multitude
93 of effects, safe and effective interventions are required.

94 Guidelines for treating depression in people with MS suggest that a combination of
95 psychological and pharmaceutical interventions is the most effective therapy in reducing

1
2
3 96 levels of depressive symptoms^{10 11}. Specifically, these guidelines recommend
4
5 97 pharmacotherapies such as antidepressants, psychological treatments such as cognitive
6
7 98 behavioural therapy, and, where applicable and safe, exercise-based interventions¹¹.
9
10 99 However, some interventions, including third wave cognitive and behavioural (psychological)
11
12 100 interventions that emphasise the role of mindfulness¹² and specific types of exercise such as
13
14 101 Pilates¹³, have not been included in these guidelines. The American Association of
15
16 102 Neurology review to inform guidelines¹⁴ noted the scarcity of trials to treat depression in
17
18 103 people with MS and therefore a lack of strong evidence. Following this review¹⁴, several
19
20 104 studies have sought to address the treatment of depressive symptoms in MS. Evidence from
21
22 105 systematic reviews reported that exercise^{15 16} and mindfulness-based interventions¹⁷ when
23
24 106 compared to waitlist/usual care have a moderate effect at reducing depressive symptoms in
25
26 107 people with MS. However, it is unclear how these interventions compare in terms of efficacy
27
28 108 and safety.

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33
34 109 Network meta-analysis enables the comparison of multiple interventions by simultaneously
35
36 110 combining direct and indirect evidence¹⁸. Synthesising the evidence in this manner will
37
38 111 enable a comprehensive understanding of how interventions compare (in terms of efficacy and
39
40 112 safety), which should greatly enhance evidence-based decision making for people with MS
41
42 113 and their clinicians on how best to manage depressive symptoms. The major assumption
43
44 114 underpinning network meta-analysis methods ensures that we can compare two interventions
45
46 115 via a third (common) intervention and is referred to as transitivity. Transitivity requires that
47
48 116 the trials included in the network meta-analysis are considered to be ‘jointly randomisable’,
49
50 117 that the common intervention (comparator) from the different trials is similar enough to be
51
52 118 combined, and that the characteristics associated with the effect of the intervention are similar

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3 119 across the included trials^{19 20}.
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6
7 120 This article outlines the protocol for a systematic review and network meta-analysis to
8
9 121 compare the effectiveness and safety of intervention modalities, or combination of modalities,
10
11 122 in reducing depressive symptoms in adults with MS. This review is the first stage of a larger
12
13 123 project that aims to provide guidance for public health researchers on the design and analysis
14
15 124 of systematic reviews with network meta-analysis and future trials in MS.
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18

19 20 125 **METHODS** 21 22

23
24 126 This systematic review protocol is registered with The International Prospective Register of
25
26 127 Systematic Reviews (PROSPERO) (CRD42020209803) and adheres to the Preferred
27
28 128 Reporting Items for Systematic Reviews and Meta-Analyses extension for Network Meta-
29
30 129 Analysis (PRISMA NMA) statement ²¹, see supplementary file 1 for checklist.
31
32
33

34 130 **Patient and public involvement** 35 36 37

38 131 Neither patients nor the public were involved in the design, conduct, or reporting of the
39
40 132 research in this article.
41
42
43

44 133 **Eligibility criteria** 45 46

47 134 **Participants** 48 49

50 135 Adults (aged 18 years or older) of any gender who have been diagnosed with any type of MS.
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52
53

54 136 **Interventions** 55 56 57 58 59 60

1
2
3 137 We will include interventions that aim to alleviate depressive symptoms in people with MS,
4
5 138 including:

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7
8
9 139 *Psychological interventions* delivered with the intention of treating depressive symptoms,
10
11 140 informed by psychological theories or principle(s) and a) implemented by a
12
13 141 psychiatrist/psychologist or other mental health clinician or b) manualized, with content
14
15 142 developed by a mental health clinician or researcher, e.g., online/app or web-based
16
17 143 intervention.

18
19
20
21
22 144 *Pharmaceutical interventions* that involve the use of medication or drugs for the intention of
23
24 145 treating depressive symptoms at a therapeutic dose according to the manufacturer guidelines
25
26 146 (if available).

27
28
29
30
31 147 *Physical interventions* including physiotherapy and physical activity (any bodily movement
32
33 148 that results in energy expenditure) including exercise, aimed at treating depressive symptoms.
34
35 149 Subtypes of physical activity will be included.

36
37
38
39 150 *Electromagnetic stimulations* involve the use of targeted electromagnetic stimulation to
40
41 151 stimulate areas of the brain to reduce depressive symptoms. Subtypes include transcranial
42
43 152 magnetic stimulation, and transcranial direct current stimulation.

44
45
46
47 153 Combinations of the above-mentioned intervention modalities will be included and will form
48
49 154 new categories. Any interventions that are specific to people with treatment resistant
50
51 155 depression/refractory depression will not be included (e.g., electroconvulsive therapy). These
52
53 156 treatments will be excluded because they will compromise the transitivity assumption (i.e.,
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1
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3 157 that all interventions are considered to be ‘jointly randomisable’). Treatments for people with
4
5 158 treatment resistant depression would not be considered to meet this assumption because they
6
7
8 159 are not considered first line treatments for people with MS¹⁸.
9

10
11 160 Grouping of interventions will depend on the eligible trials. The four broad categories will be
12
13
14 161 split into smaller sub-categories, e.g., psychological interventions could have a sub-category
15
16 162 of mindfulness-based interventions, similarly pharmaceutical interventions could have a sub-
17
18 163 category of serotonin reuptake inhibitors.
19

20 21 22 164 Comparator 23

24
25
26 165 We will consider the following comparators: any intervention modality included in the above
27
28 166 list, placebo, wait-list control, treatment as usual, or no treatment. Classification of comparator
29
30
31 167 groups will depend on the type of comparator used in the original randomised trial. Common
32
33 168 types of comparators can include, but are not limited to, placebo, wait-list control, treatment
34
35 169 as usual, and no treatment control. These comparator groups do not have similar methodology
36
37 170 and can influence participant outcome in altering ways. Therefore, for this protocol and
38
39
40 171 subsequent systematic review and network meta-analysis, we will adopt the recommended
41
42 172 framework for classification of comparator groups²². The groups will be (1) minimal
43
44 173 treatment control, active control, or similar; (2) wait-list control, treatment as usual, or no
45
46 174 treatment; and (3) pill placebo.
47
48
49

50 51 175 Outcome 52

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54 176 We will include trials that specified that depressive symptoms were the primary (or only)
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3 177 outcome, or as a secondary outcome where an *a-priori* power calculation was provided. The
4
5 178 severity of depressive symptoms must have been measured by a validated self-report
6
7
8 179 questionnaire or by clinician interview. Although depression and depressive symptoms are
9
10 180 likely to be measured and defined differently across trials ²³, we have chosen to accept all
11
12 181 types of standardised measures or clinical interviews. To assess the acute efficacy of the
13
14
15 182 intervention, depressive symptoms must be measured within two weeks of completion of the
16
17 183 intervention. We will also assess the long-term efficacy of the intervention using trials that
18
19 184 have measured depressive symptoms at approximately six months post-intervention (within 4-
20
21 185 8 months). To measure long term efficacy and safety of interventions for reducing depressive
22
23 186 symptoms we will also extract the relevant data that is measured 12 or more months post-
24
25
26 187 intervention. Any trials that have measured just one of the aforementioned time points will
27
28 188 still be eligible for inclusion.

30
31
32 189 Safety and tolerability outcomes will include:

- 33
34
35
36 190 - Frequency of serious adverse events (SAEs) defined as an untoward occurrence of a medical
37
38 191 event that is fatal, life-threatening, requires hospitalisation or prolonging of existing
39
40 192 hospitalisation and/or persistent disability ²⁴⁻²⁷.
- 41
42
43 193 - Frequency of adverse events (AEs) defined as the occurrence of an undesirable event
44
45 194 occurring during the study duration even if the event was not considered to be related to the
46
47 195 intervention ²⁴⁻²⁷.
- 48
49
50 196 - Tolerability of the intervention will be assessed as the number of participants who
51
52 197 discontinue the study and/or have reduced compliance due to SAE or AEs ^{24 28}.

53
54
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56 198 The events will be measured as dichotomous outcomes during the intervention period. We
57
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1
2
3 199 will consider combining the SAE's and AE's if they are rare events in the trials.
4
5

6 7 200 Types of Studies 8 9

10 201 We will include randomised controlled trials, including multi-arm randomised trials. Quasi-
11
12 202 randomised, cluster and cross-over trials will not be included.
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15

16 17 203 **Search strategy** 18 19

20 204 We will search the following seven databases: EMBASE, Medline, Cochrane CENTRAL,
21
22 205 APA PsycInfo, Web of Science, CINAHL and PEDro. Note that EMBASE, Medline,
23
24 206 Cochrane CENTRAL and APA PsycInfo will be searched through the Ovid platform. The
25
26 207 search strategy was developed in conjunction with a medical librarian at the University of
27
28 208 Melbourne, Australia, as well as a clinical physiotherapist (YL) who works with people with
29
30 209 MS, and a clinical psychologist (AM). The search terms relate to three main concepts of MS,
31
32 210 depression, and randomised controlled trials. Search strategies for all databases are listed in
33
34 211 supplementary file 2. All databases were searched from inception to the 11th of July 2020 and
35
36 212 the search will be updated to include articles published up to the 31st of December 2021. We
37
38 213 will also search the reference lists of relevant systematic reviews to identify any randomised
39
40 214 trials that might have been missed in the database search. Trials will be limited to those
41
42 215 published in English.
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49

50 216 **Study selection** 51 52

53 217 Results from the search strategy will be uploaded to Endnote ²⁹ where duplicates will be
54
55 218 removed. The remaining citations will be uploaded into the software management system
56
57
58
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60

1
2
3 219 Covidence³⁰ where any additional duplicates will be removed. Covidence will then be used
4
5 220 for title and abstract screening and full text screening by at least two independent reviewers
6
7
8 221 with any conflicts resolved by a third reviewer.
9

10 11 222 **Data Extraction**

12
13
14
15 223 Data will be extracted using a data extraction tool developed for this review using Excel
16
17 224 software by at least two independent reviewers, with conflicts resolved by a third reviewer. If
18
19 225 data were missing from the published article the corresponding author will be contacted. We
20
21 226 will not look at other sources of citations such as grey literature, clinical trial registries, or
22
23 227 protocol papers. The extracted data will relate to the following categories:
24
25

- 26
27
28 228 - Study characteristics: first author's last name, year of publication, year of baseline
29
30 229 recruitment, method of recruitment, method of randomisation, inclusion criteria (e.g., a
31
32 230 baseline level of depression cut off for inclusion into study).
33
34 231 - Sample demographics: sample size, number of participants randomised, baseline
35
36 232 characteristics such as diagnosis of MS, age (years), sex, years since diagnosis of MS, level of
37
38 233 disability, and disability tool.
39
40 234 - Intervention and comparator characteristics: type, frequency of intervention/treatment,
41
42 235 duration of intervention/treatment, and dose of intervention/treatment. We will use TIDieR for
43
44 236 clear reporting of the characteristics of the interventions and comparators³¹.
45
46 237 - Efficacy outcome data: type of outcome measurement scale, mean and standard deviation of
47
48 238 depressive symptom score at baseline, post-intervention, at six months post-intervention, and
49
50 239 at 12 months post-intervention (if available).
51
52 240 - Safety and tolerability data: type and number of SAEs and AEs, number of participants that
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3 241 discontinue participation due to an SAE or AE or discontinue participation for other reasons
4
5 242 during the intervention. Safety and tolerability data will be extracted for each trial arm and
6
7 243 time point where available.

8
9
10 244 - Data relating to the risk of bias assessment: randomisation process, allocation concealment,
11
12 245 deviations from intended treatment, baseline characteristics differences, missing outcome
13
14 246 data, appropriateness of outcome measurement, potential influence in outcome assessment,
15
16 247 and selectively reporting results.
17
18

19 248

20 21 249 **Risk of bias assessment**

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23
24
25 250 We will use the RoB 2 to assess the risk of bias for each study that meets the eligibility criteria
26
27 251 ³². This tool evaluates the risk of bias in five key domains: randomisation process, deviations
28
29 252 from intended interventions, missing outcome data, measurement of the outcome, and
30
31 253 selection of the reported result. The RoB 2 tool provides an overall assessment of the risk of
32
33 254 bias in the study using three categories: low risk, some concerns or high risk of bias. At least
34
35 255 two independent reviewers will assess the risk of bias in each study with any conflicts
36
37 256 between judgements resolved by a third reviewer. In this systematic review and network meta-
38
39 257 analysis there will be an inherent difference in the overall risk of bias between trials due to the
40
41 258 type of intervention. Blinding of the participants to the assigned intervention is difficult in
42
43 259 some study designs and interventions. For example, in a trial that randomised participants to
44
45 260 exercise and wait-list control, participants will be aware of the treatment arm that they were
46
47 261 allocated to. However, in a trial that randomised participants to an anti-depressant and
48
49 262 placebo, participants are unlikely to be aware which treatment they were allocated. As well,
50
51 263 blinding of the outcome assessors can also be difficult in these trials as depressive symptoms
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264 are typically measured using self-reported tools. Despite this inherent difference we have
265 chosen not to deviate from the protocol of the RoB 2 tool or alter the tool in any way.

266 **Data synthesis**

267 Characteristics of the included trials

268 We will generate descriptive statistics for the sample populations to understand the
269 demographics of the review participants across all eligible trials. These descriptive statistics
270 will describe key clinical and methodological characteristics such as age, sex, type of MS, and
271 type of intervention modality.

272 Outcome data

273 We will have two primary and two secondary outcomes.

274 *Primary outcomes:*

- 275 (1) efficacy of the interventions (reduction of depressive symptoms) measured
276 immediately post-intervention and quantified using standardised mean difference³³, and
- 277 (2) safety of the interventions (SAEs, AEs and tolerability) measured immediately post-
278 intervention and quantified using odds ratios.

279 *Secondary outcomes:*

- 280 (1) efficacy of the interventions (reduction of depressive symptoms) measured
281 immediately six months post-intervention (between four and eight months) and quantified

1
2
3 282 using standardised mean differences;
4

5 283 (2) safety of the interventions (SAEs, AEs and tolerability) measured six months post
6

7
8 284 intervention (between four and eight months) and quantified using odds ratios;
9

10 285 (3) efficacy of intervention (reduction of depressive symptoms) measured 12 months post-
11

12 286 intervention (12 months or longer) and quantified using standardised mean differences;
13

14 287 (4) safety of interventions (SAEs, AEs and tolerability) measured 12 months post-
15

16 288 intervention (12 months or longer) and quantified using odds ratios.
17
18

19 289

20
21 290 Pairwise Meta-analysis
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23

24
25 291 First, we will pool the data that compare the same major category of intervention modality
26

27 292 (i.e., psychological, pharmaceutical, physical, electromagnetic stimulation therapies or
28

29 293 combination) to each other or to placebo/usual care by fitting a random effects pairwise meta-
30

31 294 analysis model and using the restricted maximum likelihood estimator to estimate the between
32

33 295 study heterogeneity. The random effects model will assume that the underlying intervention
34

35 296 effects across the trials are similar but not identical allowing an estimation of the
36

37 297 heterogeneity in the model³⁴. This will be performed for both the efficacy outcome, using the
38

39 298 standardised mean difference, and the safety outcome, using odds ratios. Effect sizes will be
40

41 299 presented with their corresponding 95% confidence intervals. Heterogeneity will be estimated
42

43 300 using the I^2 and τ^2 statistics³⁵.
44
45

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47
48
49 301 Network meta-analysis model
50

51
52
53 302 We will fit a multivariate meta-analysis contrast-based model within a frequentist framework
54

55 303 using the network package in Stata³⁶. We will assume common heterogeneity across the
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1
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3 304 trials.
4
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6
7 305 Geometry of the network
8
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10 306 We will generate a network diagram, separately for efficacy and safety, to visualise the
11
12 307 network of intervention modalities. The nodes (or intervention modalities) will represent the
13
14 308 total number of trials in each treatment group; the larger the size of the node the larger the
15
16 309 sample size. The edges of the lines connecting each node will represent the precision of the
17
18 310 evidence, i.e., the thicker the line the more precise evidence. Figure 1 shows an example of the
19
20 311 possible network structure with the major intervention modalities included.
21
22
23
24

25
26 312 **<insert figure 1 here>**
27
28
29

30 313 Assessment of transitivity in the network
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32

33
34 314 The transitivity assumption, which underpins the method of a network meta-analysis, requires
35
36 315 that the characteristics associated with the effect of the intervention are similar across the
37
38 316 included trials¹⁸. Participant characteristics (for example, age, sex, type of MS, level of
39
40 317 disability, and years since diagnosis of MS) could indicate violation of the transitivity
41
42 318 assumption¹⁸. To assess this requirement of the transitivity assumption the characteristics of
43
44 319 the participants recruited into each trial will be summarised and compared. If this requirement
45
46 320 of the transitivity assumption is thought to be violated, we will undertake narrative synthesis
47
48 321 of the data (described below) and possibly pair wise meta-analyses (described above). If we
49
50 322 find no reason to suggest that violation of the transitivity assumption, we will synthesise the
51
52 323 available evidence using network meta-analysis techniques. We will fit a random effects
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3 324 network meta-analysis model in a frequentist framework and assume a common heterogeneity
4
5 325 parameter across the eligible trials. The random effects model assumes that the variation
6
7 326 between trials could be a result of heterogeneity and not from sampling variation^{18 36}.

11 327 Summary Statistics and presentation of results

15 328 We will present forest plots that will include pooled estimates from the direct and mixed
16
17 329 intervention effects and league tables with the summary standardised mean differences or
18
19 330 odds ratios for all pairwise comparisons^{37 38}. We will use a predictive interval plot to show the
20
21 331 grouped intervention modality standardised mean differences or odds ratios in a future trial³⁷.
22
23 332 We will then obtain a hierarchy of the intervention modalities using the surface under the
24
25 333 cumulative ranking curve (SUCRA). SUCRA uses probabilities to determine which
26
27 334 intervention modality is most likely to be the most effective at reducing depressive symptoms
28
29 335 in people with MS. A probability of 1 (or 100%) is indicative of the stated intervention
30
31 336 modality being the most effective intervention modality, conversely, a probability of 0 (or 0%)
32
33 337 is indicative of the stated intervention modality being the least effective³⁸.

40 338 Assessment of inconsistency

43 339 Consistency is a measure of the agreement between direct evidence and indirect evidence. If
44
45 340 inconsistency occurs in a network it may suggest that there is significant heterogeneity and
46
47 341 that the transitivity assumption could be violated^{18 34}. Using the network meta-analysis
48
49 342 package in Stata³⁶ a consistency and an inconsistency model can be separately fitted to assess
50
51 343 whether the direct and indirect evidence are in agreement for each outcome. These models can
52
53 344 provide information to help ascertain if the direct and indirect evidence are in statistical

1
2
3 345 agreement³⁹. If there is evidence of inconsistency in the network, we will use the side-
4
5 346 splitting approach to identify if there is a specific modality of interventions that contribute to
6
7 347 inconsistency in the network^{36,39}. This will enable us to further investigate the possible
8
9 348 sources of inconsistency⁴⁰.

14 349 Subgroup analysis

17
18 350 We will conduct separate subgroup analyses for the efficacy and the safety outcome if there is
19
20 351 substantial heterogeneity or inconsistency and the data allows this.

23
24 352 For the efficacy outcome, we will assess the following subgroups:

- 27 353 – Year of baseline recruitment; to determine if treatments have become more
28
29 354 effective over time.
- 31 355 – Severity of depression at baseline (i.e., trials that recruited based on level of
32
33 356 depression vs trials that did not); to determine whether interventions are efficacious
34
35 357 when a level of depressive symptoms is present.
- 38 358 – Comparison of self-reported outcome measures vs clinical assessment; to
39
40 359 determine if there is a difference in the efficacy of the treatment due to the
41
42 360 measurement of the outcome.
- 45 361 – Level of disability at enrolment (e.g., as measured by Patient determined disease
46
47 362 steps, Expanded Disability Disease Scale: categorised in mild, moderate or severe
48
49 363 disability); to determine if level of disability is associated with the efficacy of the
50
51 364 intervention.
- 54 365 – Whether the intervention was conducted in a dose according to guidelines that

1
2
3 366 exist for that type of interventions (e.g., exercise guidelines for people with MS);
4
5 367 to determine if a minimum dose is associated with the efficacy of the intervention.
6
7

8 368 For the safety and tolerability outcome we will undertake subgroup analyses by year of
9
10 369 baseline recruitment and level of disability at enrolment.
11

12 370

13
14 371 Assessment of small study effects
15

16
17
18 372 We will use the comparison-adjusted³⁷ and contour-enhanced⁴¹ funnel plots to investigate
19
20 373 whether results in imprecise trials differ from those in more precise trials. Network meta-
21
22 374 regression models will be used to investigate associations between study sample size and
23
24 375 effect size⁴².
25
26
27
28

29 376 Narrative synthesis
30

31
32
33 377 If we are unable to conduct a NMA or pairwise meta-analyses we plan to conduct a narrative
34
35 378 synthesis to assess which interventions reported the outcomes of interest and if there were any
36
37 379 patterns relating to specific interventions, or gaps in the literature.
38
39
40

41 380 **ETHICS AND DISSEMINATION**

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43
44

45 381 Ethical approval is not needed for a systematic review and network meta-analysis as we will
46
47 382 use aggregated data from previously published randomised trials. The dissemination of the
48
49 383 results of the systematic review and network meta-analysis will include publishing in a peer
50
51 384 reviewed journals to apprise MS researchers and clinicians, and people with MS. The results
52
53 385 of the systematic review and network meta-analysis have the potential to inform future
54
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2
3 386 treatment guidelines for depression in people with MS. Further, the review may highlight any
4
5 387 gaps in the literature and provide recommendations for the conduct and reporting of future
6
7
8 388 randomised trials.
9

10 11 389 **AUTHORS CONTRIBUTIONS**

12
13
14
15 390 AK and CHM conceived the study. AK, CHM, JL, SC, YL, AGK and AM contributed to the
16
17 391 study design. JL drafted the manuscript and AK, CHM, SC, YL edited the manuscript. All
18
19
20 392 authors read and approved the final manuscript.
21
22

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25
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27
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29
30
31 396 (ID 20-216).
32

33 397 **CONFLICT OF INTEREST**

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35
36
37 398 The authors declare no conflict of interest.
38
39

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41 525 Figure 1: The possible network structure for the major categories of interventions. Comparator
42 526 group(s) may be split into multiple nodes as outlined in the comparator group section.
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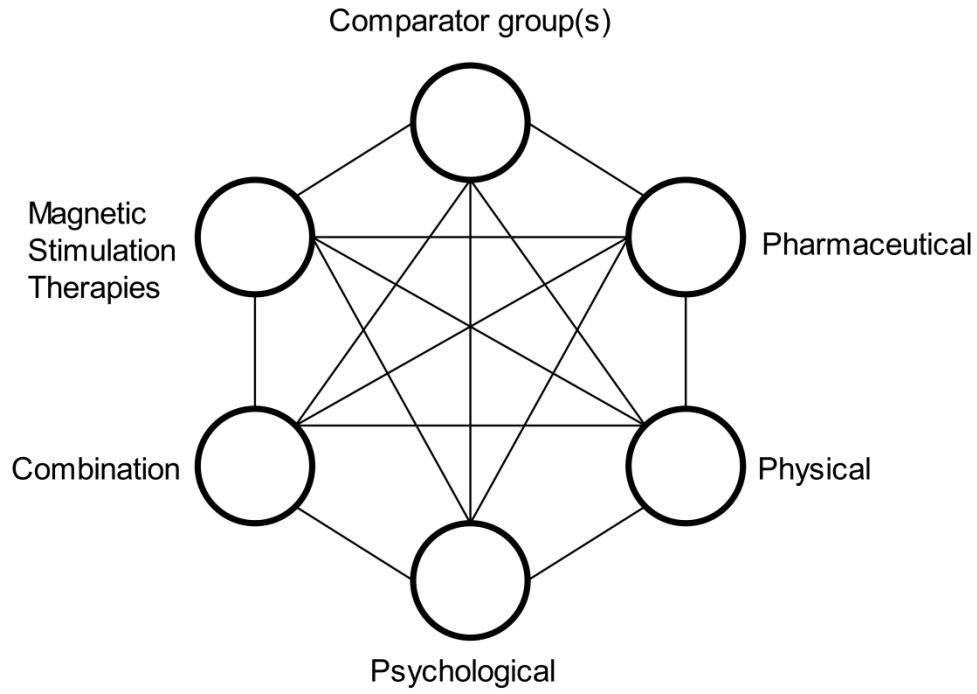


Figure 1: The possible network structure for the major categories of interventions. Comparator group(s) may be split into multiple nodes as outlined in the comparator group section.

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SUPPLEMENTARY FILE 1:

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Table 1: PRISMA-NMA guidelines checklist.

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PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	6-10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	Supplementary file

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1			including any limits used, such that it could be repeated.	
2	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	10-11
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7	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	11-12
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10	Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11-12
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13	Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	15
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20	Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	12-13
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25	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	16
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31	Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i> 	14-18
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40	Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	15-16
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44	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	18
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47	Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network; and</i> • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i> 	17-18
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1	Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	NA
2				
3	Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	NA
4				
5	Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	NA
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11	Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA
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14	Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	NA
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17	Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	NA
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22	Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	NA
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31	Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	NA
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36	Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	NA
37				
38	Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses</i> , and so forth).	NA
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60**DISCUSSION**

Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	NA
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	NA
FUNDING			19
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this

SUPPLEMENTARY FILE 2:

Complete database search strategy

Supplementary Table 1: Search strategy for databases EMBASE, APA PsycInfo, MEDLINE, Cochrane CENTRAL, searched through the Ovid platform.

	Search terms
1	multiple sclerosis.ti,ab.
2	exp multiple sclerosis/
3	1 or 2
4	exp depression/
5	(depress* or mood disorder or despair or misery or unhappiness or dysthymia or dysphor* or seasonal affective disorder or affective disorder or sadness or loss of pleasure).ti,ab.
6	4 or 5
7	exp randomized controlled trial/
8	("random* control* trial*" or RCT or "random-allocation*" or "random allocation*" or "double-blind*" or "double blind*" or "single-blind*" or "single blind*" or mask* or random* or "control* stud*" or "control* clinical trial*" or "comparative stud*").ti,ab.
9	7 or 8
10	3 AND 6 AND 9

Supplementary Table 2: Search strategy for databases CINAHL through the Scopus platform*, and Web of Science searched through the Web of Science platform*.

	Search Term
1	“multiple sclerosis”
2	depress* or “mood disorder*” or despair or misery or unhappiness or dysthymia or dysphor* or “seasonal affective disorder” or “affective disorder” or sadness or “loss of pleasure”
3	("random* control* trial*" or RCT or "random-allocation*" or "random allocation*" or "double-blind*" or "double blind*" or "single-blind*" or "single blind*" or mask* or random* or "control* stud*" or "control* clinical trial*" or "comparative stud*")
4	1 AND 2 AND 3

*The search strategy for Scopus platform and Web of Science platform is the same.

Supplementary Table 3: Search strategy for PEDro database.

	Search line
1	“multiple sclerosis” and depress*

For peer review only