Reporting interventions in trials evaluating cognitive rehabilitation in people with Multiple Sclerosis: A systematic review

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Abstract

Objective: To determine the quantity and quality of description of cognitive rehabilitation for cognitive deficits in people with Multiple Sclerosis, using a variety of published checklists, and suggest ways of improving the reporting of these interventions.

Data sources: Ten electronic databases were searched, including MEDLINE, EMBASE, CINAHL and PsycINFO, from inception to May 2017. Grey literature databases, trials registers, reference lists and author citations were also searched.

Review methods: Papers were included if participants were people with multiple sclerosis aged 18 years and over, and if the effectiveness of cognitive rehabilitation in improving functional ability for memory, attention or executive dysfunction, with or without a control group, was being evaluated.

Results: Fifty-four studies were included in this review. The reporting of a number of key aspects of cognitive rehabilitation was poor. This was particularly in relation to content of interventions (reported completely in 26 of the 54 studies), intervention procedures (reported completely in 16 of the 54 studies), delivery mode (reported completely in 24 of

the 54 studies) and intervention mechanism of action (reported completely in 21 of the 54 studies).

Conclusion: The quality of reporting of cognitive rehabilitation for memory, attention and executive function for multiple sclerosis, across a range of study designs, is poor. Existing reporting checklists do not adequately cover aspects relevant to cognitive rehabilitation, such as the approaches used to address cognitive deficits. Future checklists could consider these aspects we have identified in this review.

Keywords: Cognitive rehabilitation, multiple sclerosis, systematic review, quality of reporting, description of interventions.

Introduction

Although the effectiveness of cognitive rehabilitation programmes for people with multiple sclerosis has been evaluated in previous trials[1-4] and systematic reviews,[5, 6] researchers have often not provided sufficient details of the interventions. Following the International Classification of Functioning, Disability and Health (ICF)[7] core sets for the focus of rehabilitation in relation to multiple sclerosis,[8] cognitive rehabilitation can be defined as a structured set of therapeutic cognitive activities designed to address cognitive deficits by using a range of approaches to improve individuals' everyday functional abilities and promote independence.

Precise and complete descriptions of interventions are needed in rehabilitation research to facilitate replication of the intervention by other researchers, and to enable implementation into clinical practice.[9] This has been emphasised by Michie and colleagues[10] who have stressed the need for greater transparency in reporting complex interventions, and have

underlined the need for the salient effective components or the 'active ingredients' to be clearly described in research studies.[10]

Two previous reviews found that information relating to treatment dose, delivery format and information about the staff who delivered the intervention[11] and session by session content[12] were poorly reported in trials of cognitive rehabilitation for a range of neurological conditions. Both reviews suggested developing a checklist for reporting interventions in a standardised way, as a standalone[11] or to be used as an adjunct[13] to the Template for Intervention Description and Replication (TIDieR)[14] checklist for researchers. As TIDieR is a general tool for pharmacological and non-pharmacological studies, specific aspects of cognitive rehabilitation (e.g., group size, take home activities) could be omitted even when following this checklist.

A major limitation of previous reviews and checklists is that by only including RCTs and a range of non-specific neurological conditions, the findings do not provide a comprehensive overview of research into cognitive rehabilitation for people with multiple sclerosis. The findings of Mitolo and colleagues[15] suggest there are potentially more studies that could inform the development of a reporting checklist for cognitive rehabilitation specifically for multiple sclerosis.

The limitations within existing systematic reviews implies a more exhaustive examination of what is currently reported about cognitive interventions for people with multiple sclerosis is needed. This would strengthen the validity of existing cognitive rehabilitation checklists. Therefore our primary aim was to conduct a systematic review specifically focused on the

description cognitive rehabilitation interventions used for people with multiple sclerosis. The focus was interventions targeting memory, attention and executive function, some of the most commonly reported problems in multiple sclerosis.[16-18] The secondary aims were to evaluate the quality of reporting of interventions, and to make recommendations on how to improve the reporting of cognitive interventions.

Methods

We conducted this review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] We only included studies with people aged 18 years and over, with any type of multiple sclerosis. We included studies involving participants with other neurological disorders (e.g. stroke) if a subgroup of people with multiple sclerosis could be identified or the sample had a substantial number (defined as at least 75% of the participants). We included studies that were a re-analysis or subgroup analysis, or a sub-study of an included primary study.

We included any study that evaluated interventions for memory, attention and executive function in people with multiple sclerosis, with or without a control group. We defined cognitive rehabilitation as a structured set of therapeutic cognitive activities that aimed to improve function and participation in daily activities.[7, 8] The interventions had to occur over more than one session, were delivered in any setting (e.g., hospital or home-based) and in any format (e.g., computer-based, face-to-face, group-based, blended and one-to-one interventions).

We included studies where the primary or secondary outcomes were measures of functional ability. These could be objective neurocognitive/neuropsychological measures (batteries/tests), or self-report measures that assess memory, attention and executive function problems in everyday life. We also included studies reporting outcomes assessing mood, fatigue and general function, to account for the relationship these variables have with self-reported cognitive impairments, and the effect that this has on quality of life.[17, 20] We did not restrict the search strategy by date or geographical location, but excluded studies not published in English.

We conducted searches across a number of electronic databases and set up alerts to highlight new papers published in-between the initial search and the analysis. We developed a search strategy for MEDLINE (Ovid) based on the aforementioned inclusion and exclusion criteria (see Supplementary Data File 1), and modified it for other databases.

The following ten databases were searched from time of inception to May 1st 2017: MEDLINE In-Process & Other Non-Indexed Citations (1946 to current); EMBASE (1974 to current); CINAHL (1982 to current); Applied Social Sciences Index and Abstracts (ProQuest) (1987 to current); ISI Web of Science: Social Sciences Citation Index (1956 to current); PsycINFO (1806 to current); Dissertations & Theses A&I (1743 to current); Dissertations & Theses - UK and Ireland (1716 to current); Allied and Complementary Medicine database (1985 to current); CAB Abstracts (1973 to current).

The reference lists of all included studies and previously published reviews[5, 6, 15] were searched for relevant studies. The Cochrane Central Register of Controlled Clinical Trials (CENTRAL) (The Cochrane Library, latest issue) was searched to identify other relevant systematic reviews. We hand-searched the UK Clinical Trials Gateway (https://www.ukctg.nihr.ac.uk/), NIHR Clinical Research Network database, and Networked Digital Library of Theses & Dissertations. We also searched the specialist register GreyNet (http://www.greynet.org/) for grey literature.

The first author (JMM) judged the eligibility of the studies by assessing the titles and abstracts against the pre-defined inclusion criteria. We developed a hierarchy (Supplementary Data File 2) for exclusion. Two reviewers (JMM and OAK) obtained full text copies of all potentially relevant studies or studies where there was uncertainty regarding their inclusion, and independently assessed whether they met the inclusion criteria. Any disagreements were resolved by discussion with a third reviewer (RdN).

Two reviewers (JMM and OAK) extracted data pertaining to the theory and underlying assumptions of the interventions, and descriptions of cognitive rehabilitation. We also included relevant items from checklists identified in the literature and applicable to cognitive rehabilitation research. We included items from the TIDieR checklist, systematic reviews by Martin[12] and van Heugten,[11] American Psychological Society's publication manual's Journal Article Reporting Standards[21] and Western Journal of Nursing Research[22] checklist for the reporting of interventions. Where multiple reports contained varying descriptions of the content of the same interventional study, this was recorded. Data from

multiple reports were not combined into a single data collection form, nor was information from multiple forms combined at this stage.

The various components of the intervention described in each paper were coded against the checklists and frameworks. Content was recorded as complete (based on the description provided for each item), partially reported, or missing. A third reviewer (RdN) checked a random selection (10%) of the data entered. Where corrections were required, we conducted a full audit trail to understand why the error had occurred. As the aim of the review was to report on how interventions were reported, we did not contact study authors to request additional or missing data. A narrative synthesis process [23] was followed for data analysis.

Results

Figure 1 provides a flowchart illustrating the search process. Supplementary Data File 3 provides details of the 54 included studies. The cognitive domains targeted in the rehabilitation programmes of the included studies are presented in Table 1.

Where similar items from different checklists were identified (that is, describing the same reporting information) the results of the coding/data extraction were merged (Supplementary Data File 4). Table 2 presents a summary of the findings of the quality of reporting of the included studies based on the merged checklist items.

Overall quality of reporting of interventions

Information relating to the characteristics of the participants (such as baseline demographic and clinical characteristics) was reported completely in the majority of the included papers (n=51; 94%).

Intervention details that were reported partially complete

Who delivered the intervention?

The individuals who delivered the intervention were mostly described by their professional training (n=19; 82%), with the majority being rehabilitation psychologists, psychologists or neuropsychologists.

If the individual who delivered the intervention was reported to have received training (n=4; 17%), no further information was provided. For example, one paper reported that "the facilitator (interventionist) was a master's prepared nurse carefully trained prior to the initiation of the study".[2 (p. 884)] None of the papers provided any details regarding the therapists' competency level to deliver the intervention.

The intervention 'dose'

The frequency of sessions (n=50; 93%), total number of sessions (n=33; 61%), and duration of the intervention (n=50; 93%) was often reported. However, the actual dose (what actually happened) was missing. Only 17 (32%) papers provided this information (e.g., in the form of descriptive statistics).

The key elements of the intervention, including active ingredients and mechanism of action

Only two papers made specific reference to the active ingredients of the intervention. For example one paper reported the following: “The only difference between the groups was that only the treatment group was exposed to the active ingredients of the mSMT (imagery and context)”.[24 (p. 2067)] Twenty-one (39%) papers reported the key elements of the intervention and the intended mechanism of action, but did not make explicit mention of active ingredients. For example, one paper defined the intervention as: “ProCog-SEP program […] based on exercises drawn from facilitation/reorganization theories. This technique is defined by the use of preserved functions. It aims to teach the patient to use facilitation strategies to help these preserved functions, like mental imagery, or semantic cues”.[25 (p. 554)]

The majority (n=29; 54%) of the studies indicated the cognitive rehabilitation strategy, but did not specify the intended mechanism of action or goal of the key elements. For example one paper-reported: “[…] this investigation focused specifically on training processing speed and working memory, the most fundamental cognitive deficits for multiple sclerosis patients”.[26 (p. 114)]

Procedures

Specific details about the procedures (e.g., ‘the methods section of a recipe’) as described in the TIDieR[14] checklist were only complete in 16 (30%) papers. This information was incomplete in 36 (67%) of the papers. Information that was often incomplete or missing included session-by-session content and the format of the sessions.

Materials

The intervention materials were reported completely in 12 (22%) papers. For instance, one paper included an example of the patient score sheet used for one of the rehabilitation sessions. In 32 (59%) papers the materials were not mentioned specifically, but could be inferred from the procedures. Ten (18%) papers did not provide this information.

Intervention details that were reported poorly

Intervention mode of delivery

The mode of intervention delivery (delivered individually or in a group) was often not clear. Only 24 (44%) papers mentioned this explicitly. In eight (15%) papers the delivery mode could be deduced if information about the setting (e.g., home-based) or format (e.g., computer-based) was reported. For example, one paper reported that the intervention was delivered in the participants' homes, therefore, we assumed that the intervention was individually delivered. Details pertaining to the intervention mode of delivery were not reported in 22 (41%) papers.

Specific to group interventions

The minimum and maximum number of people in the groups was only reported in one of the 14 group-based or blended studies. Four (29%) studies reported the maximum number of people in each group. The group size was not reported in nine (64%) papers.

Multiple study reports

There were mixed findings when the quality of reporting was compared across several studies reporting the same intervention. For example, more details about the procedures (including how missed sessions were dealt with), the intervention dose, the location, who

delivered the intervention (i.e., professional skills and intervention-specific competencies) were provided in the one-year follow-up to the *Sclerosi Multipla Intensive Cognitive Training (SMICT)* trial[27] than in the original study[28] or the two-year follow-up study.[29] However, the quality of the reporting for another trial was observed to be consistent when comparing the primary study[30] to subsequent sub-group[31] and secondary analysis[32] of the Story Memory Technique (mSMT) intervention.

Comparison of the quality of reporting across different reporting checklists

Studies that did well on one checklist and not on others

Three papers[26, 33, 34] performed 'well' (that is, provided more complete descriptions of the intervention, based on the description provided for each item, where applicable) on the TIDieR checklist. Two papers[33, 34] reported the materials, procedures and tailoring of the intervention completely. All three papers provided partial information for who delivered the intervention. For example, papers mentioned research assistant or neuropsychologist but did not mention what, if any, training they received or how many people delivered the intervention. All three papers did not report whether the intervention was modified (e.g., changes to the intervention provider or intervention material) during the study. For all papers, partial information was reported for the intervention dose, the skills and qualifications of the person who delivered the intervention. All three papers performed poorly on the Western Journal of Nursing checklist[22], particularly for items relating to the conceptual frameworks of the intervention, intervention materials, intervention procedural items (e.g., the timing of the intervention delivery) and intervention variations. These items were the most poorly reported across all checklists.

Studies that performed well on all checklists

None of the studies performed well on all checklists, but two papers[1, 2] were close to achieving this.

Studies that did not perform well on any of the checklists

Forty-four (82%) papers provided incomplete or missing reports of the session by session content of the interventions (for example, these four papers[31, 35-37]). There was no obvious reason for this, nor commonality between the studies in this group, for instance, in terms of mode of delivery (group or individual) or type of study (primary or secondary/sub-group analyses of a primary study.

Discussion

We examined how cognitive rehabilitation for memory, attention and executive function for people with multiple sclerosis is reported in scientific journals. The review showed that, overall, the reporting of the content of cognitive rehabilitation was poor. Specifically, we found that a number of key details needed to aid replication of the study were either reported incompletely or were missing. Information that was partially reported was: the key elements of the intervention (including active ingredients and mechanism of action); the theory or conceptual framework for the intervention; details of the content, i.e., exactly what participants received; and the intervention 'dose'. Information that was reported poorly was: how the intervention was delivered; whether the intervention was delivered as planned; whether participants adhered.

There were no discernible differences in the quality of reporting of the same intervention across multiple study reports (i.e., primary study compared to follow-up and/or secondary analyses). In terms of the checklists used, none of the included papers performed well on all the checklists, with items from the Western Journal of Nursing checklist[22] tending to be reported incompletely or not at all.

Our findings are comparable with previous research that found 50 to 70 percent of non-pharmacological interventions were poorly reported.[38-40] Specifically, information relating to the theory/aims of the intervention,[12] the content and intervention procedures,[11, 12, 38, 40] the materials used,[12, 38, 40] fidelity and adherence[11] was omitted from published studies.

Complete descriptions of interventions are needed to enable replication by other researchers, and for implementation into clinical practice.[9] This viewpoint is supported by Cicerone,[41] who also argues that imprecise descriptions may lead to disagreements when interpreting the research evidence. Michie and colleagues[10] argue for the 'active ingredients' of the intervention needing to be described clearly in research studies.[10] 'Active ingredients' of a complex intervention are the components of the intervention that are "essential to achieving good outcomes for those targeted by the intervention".[10 (p. 40)] We acknowledge that in complex interventions, some of the 'active' ingredients can only be hypothesised based on theory or previous research literature. In our review, only two papers[24, 32] made specific reference to the active ingredients of their intervention, whilst 18 papers provided information on the intended mechanism of action. This is closely linked with the theory/conceptual framework upon which the interventions are based (only reported completely in 54% of the included studies). Cognitive rehabilitation is driven by

cognitive, emotion, behavioural and learning models and theories.[42, 43] However, the actual contribution of each ingredient to the overall effect of the treatment can only be understood if each of those ingredients were assessed and reported. This might be beyond the scope of some studies, and hence is not featured in many of the papers.

There is evidence that checklists can improve the quality of reporting of interventions.[44-47] However, in a recent scoping review of systematic reviews of adherence to reporting guidelines by Samaan and colleagues,[39] of the 50 included reviews, 43 (86%) reported poor levels of adherence to reporting guidelines. The authors provided a number of recommendations to improve adherence, including the use of *appropriate* reporting guidelines. Taken together with the existing literature, the findings from this review provide further evidence for the need for more domain/intervention-specific checklists.[9, 11, 12, 38-40]

Several issues came to light during the data extraction and coding process, based on the checklists used. Disparities in coding of different checklist items could be attributed to whether or not an item description was provided, and the level of description/detail provided. Where no item descriptions were supplied, it was left to the reviewers to determine what was required for a specific checklist item. Thus, items on a checklist should be accompanied with a clear and detailed description, as well as with examples.

The coding process that was undertaken in this review highlighted the need for a checklist that is user-friendly, in terms of the number of items contained within it and the way in which items are presented. We suggest a one-page checklist, whereby a tick-box is used to indicate whether a particular aspect of the intervention content has been reported.

The checklists used in this review tended to describe intervention components, such as 'dose' in more medical terminology, which would not be appropriate for some rehabilitation interventions. For example, the Journal Article Reporting Standards[21] checklist includes an item that asks researchers to report how long any effects of the intervention were intended to last. The terminology of our proposed checklist should be appropriate for cognitive rehabilitation, such as the maintenance of strategies or skills targeted in the intervention, as suggested by Sohlberg and Mateer.[48] This may help towards ameliorating the difficulty researchers face using multiple checklists in tandem to report on different aspects of their research.

Our review follows Moher and colleagues'[49] recommended steps for developing health research reporting guidelines and previous reviews by van Heugten and colleagues[11] and Martin and colleagues.[12] These two reviews examined the content of cognitive rehabilitation interventions for a range of neurological conditions, including multiple sclerosis. They also considered several cognitive domains (memory, attention, executive function, language, awareness, visuospatial functioning and apraxia) and found the overall quality of reporting was poor. This current review built on the findings of these reviews, but is unique as it focused solely on studies of the cognitive rehabilitation of memory, attention and executive function for people with multiple sclerosis.

In light of the evidence presented, a domain-specific reporting checklist (i.e., that is *appropriate*) may facilitate better reporting of the content of cognitive rehabilitation for people with multiple sclerosis. For example, the checklist could include the rehabilitation

setting (inpatient, outpatient, home-based), the practical details needed to administer the key elements of the intervention (following fundamental approaches to cognitive rehabilitation to restore cognitive function, the use compensatory strategies and devices, or environmental modifications[50]), and the materials used by both facilitators and participants.

A strength of our systematic review is the inclusion of a variety of study designs in the search strategy. This provides a more comprehensive examination of the quality of reporting of cognitive rehabilitation in multiple sclerosis compared to previous reviews. However, one potential limitation of the review is that we only included published studies of interventions for memory, attention or executive dysfunction. While 70% of published cognitive rehabilitation studies in multiple sclerosis target the cognitive domains of memory, attention and executive function[15], we acknowledge that the studies we included may not be representative of all cognitive rehabilitation research in multiple sclerosis.

Clinical messages

- Most studies do not adequately report key aspects of cognitive rehabilitation for memory, attention and executive function for people with multiple sclerosis. This may prevent implementation of cognitive rehabilitation clinically.
- Current reporting checklists may be too general, or use terminology that may not be appropriate for cognitive rehabilitation but more suited to drug trials. Therefore, modifications to these or new checklists need to take into account clinicians who deliver cognitive rehabilitation.

Conflict of interest

RdN is an author of one study that was included in this review.

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References

1. Carr SE, das Nair R, Schwartz AF and Lincoln NB. Group memory rehabilitation for people with multiple sclerosis: a feasibility randomized controlled trial. *Clin Rehabil* 2014; 28: 552-561.
2. Stuifbergen AK, Becker H, Perez F, Morison J, Kullberg V and Todd A. A randomized controlled trial of a cognitive rehabilitation intervention for persons with multiple sclerosis. *Clin Rehabil* 2012; 26: 882-893.
3. Hildebrandt H, Lanz M, Hahn HK, et al. Cognitive training in MS: effects and relation to brain atrophy. *Restor Neurol Neurosci* 2007; 25: 33-43.
4. Solari A, Motta A, Mendozzi L, et al. Computer-aided retraining of memory and attention in people with multiple sclerosis: a randomized, double-blind controlled trial. *J Neurol Sci* 2004; 222: 99-104.5. Rosti-Otajärvi EM and Hämäläinen PI. Neuropsychological rehabilitation for multiple sclerosis. *Cochrane Database of Systematic Reviews* 2014; 2.
6. das Nair R, Martin K-J and Lincoln NB. Memory rehabilitation for people with multiple sclerosis. *Cochrane Database of Systematic Reviews 2016*: Art. No.: CD008754.
7. World Health Organisation (WHO). *International Classification of Functioning, Disability and Health: ICF*. World Health Organization, 2001.
8. Beer S, Khan F and Kesselring J. Rehabilitation interventions in multiple sclerosis: an overview. *J Neuro* 2012; 259: 1994-2008.
9. Dijkers MP. Reporting on Interventions: Issues and Guidelines for Rehabilitation Researchers. *Arch Phys Med Rehabil* 2015; 96: 1170-1180.
10. Michie S, Fixsen D, Grimshaw JM and Eccles MP. Specifying and reporting complex behaviour change interventions: the need for a scientific method. *Implementation Science* 4 2009 (Accessed 03 April 2016).
10. van Heugten C, Wolters Gregório G and Wade D. Evidence-based cognitive rehabilitation after acquired brain injury: a systematic review of content of treatment. *Neuropsychol Rehabil* 2012; 22: 653-673.
12. Martin KJ, Sinclair EJ and dasNair R. Descriptions of memory rehabilitation group interventions for neurological conditions: A systematic review. *Clin Rehabil* 2015; 30: 705-713.
13. Martin KJ, Lincoln N and das Nair R. Group-based memory rehabilitation for people with multiple sclerosis: Subgroup analysis of the ReMIND trial. *Int J Ther Rehabil* 2014; 21: 590-596.
14. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014; 348: g1687.
15. Mitolo M, Venneri A, Wilkinson ID and Sharrack B. Cognitive rehabilitation in multiple sclerosis: A systematic review. *J Neurol Sci* 2015; 354: 1-9.

16. Chiaravalloti ND and DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol* 2008; 7: 1139-51.
17. Rao S, Leo G, Ellington L, Nauertz T, Bernardin L and Unverzagt F. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. Neurology 1991; 41: 692-696.
18. Guimarães J and Sá MJ. Cognitive dysfunction in multiple sclerosis. *Front Neurol* 2012; 24: 74.
19. Moher D, Liberati A, Tetzlaff J and Altman D. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 2009; 6.
20. Arnett PA and Strober LB. Cognitive and neurobehavioral features in multiple sclerosis. *Expert Rev Neurother* 2011; 11: 411-424.
21. VandenBos GR, Gasque AW and Jackson P. *Publication manual of the American Psychological Association* 6th ed. Washington DC: American Psychological Association 2010.
22. Conn VS. Unpacking the Black Box Countering the Problem of Inadequate Intervention Descriptions in Research Reports. *West J Nurs Res* 2012; 34: 427-433.
23. Popay J, Roberts H, Sowden A, et al. Guidance on the conduct of narrative synthesis in systematic reviews. *A product from the ESRC methods programme Version* 2006, p. B92.
24. Chiaravalloti ND, Moore NB, Nikelshpur OM and DeLuca J. An RCT to treat learning impairment in multiple sclerosis: The MEMREHAB trial. *Neurology* 2013; 81: 2066-72.
25. Brissart H, Leroy M, Morele E, Baumann C, Spitz E and Debouverie M. Cognitive Rehabilitation in Multiple Sclerosis. *Neurocase* 2013; 19: 553-65.
26. Hancock LM, Bruce JM, Bruce AS and Lynch SG. Processing speed and working memory training in multiple sclerosis: a double-blind randomized controlled pilot study. *J Clin Exp Neuropsychol* 2015; 37: 113-127.
27. Mattioli F, Stampatori C, Bellomi F, et al. A RCT Comparing Specific Intensive Cognitive Training to Aspecific Psychological Intervention in RRMS: The SMICT Study. *Front Neuro* 2014; 5: 278.
28. Mattioli F, Stampatori C, Zanotti D, Parrinello G and Capra R. Efficacy and specificity of intensive cognitive rehabilitation of attention and executive functions in multiple sclerosis. J *Neurol Sci* 2010; 288: 101-105.
29. Mattioli F, Bellomi F, Stampatori C, et al. Two Years Follow up of Domain Specific Cognitive Training in Relapsing Remitting Multiple Sclerosis: A Randomized Clinical Trial. *Front Behav Neurosci* 2016; 10: 28.
30. Chiaravalloti ND, DeLuca J, Moore NB and Ricker JH. Treating learning impairments improves memory performance in multiple sclerosis: A randomized clinical trial. *Mult Scler* 2005; 11: 58-68.

31. Chiaravalloti ND, Wylie G, Leavitt V and Deluca J. Increased cerebral activation after behavioral treatment for memory deficits in MS. *J Neurol* 2012; 259: 1337-1346.
32. Leavitt VM, Wylie GR, Girgis PA, DeLuca J and Chiaravalloti ND. Increased functional connectivity within memory networks following memory rehabilitation in multiple sclerosis. *Brain Imaging Behav* 2014; 8: 394-402.
33. Hanssen KT, Beiske AG, Landro NI, Hofoss D and Hessen E. Cognitive rehabilitation in multiple sclerosis: a randomized controlled trial. *Acta Neurol Scand* 2015; 133: 30-40.
34. Jonsson A, Korfitzen EM, Heltberg A, Ravnborg MH and Byskovottosen E. Effects of neuropsychological treatment in patients with multiple-sclerosis. *Acta Neurol Scand* 1993; 88: 394-400.
35. Ernst A, Blanc F, De Seze J and Manning L. Using mental visual imagery to improve autobiographical memory and episodic future thinking in relapsing-remitting multiple sclerosis patients: A randomised-controlled trial study. *Restor Neurol Neurosci* 2015; 33: 621-638.
36. Parisi L, Rocca MA, Mattioli F, et al. Changes of brain resting state functional connectivity predict the persistence of cognitive rehabilitation effects in patients with multiple sclerosis. *Mult Scler* 2014; 20: 686-694.
37. Vogt A, Kappos L, Calabrese P, et al. Working memory training in patients with multiple sclerosis - comparison of two different training schedules. *Restor Neurol Neurosci* 2009; 27: 225-235.
38. Glasziou P, Meats E, Heneghan C and Shepperd S. What is missing from descriptions of treatment in trials and reviews? *BMJ* 2008; 336: 1472-1474.
39. Samaan Z, Mbuagbaw L, Kosa D, et al. A systematic scoping review of adherence to reporting guidelines in health care literature. *J Multidiscip Healthc* 2013; 6: 169-188.
40. Hoffmann TC, Erueti C and Glasziou PP. Poor description of non-pharmacological interventions: analysis of consecutive sample of randomised trials. *BMJ* 2013; 347: f3755.
41. Cicerone KD, Dahlberg C, Malec JF, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. *Arch Phys Med Rehabil* 2005; 86: 1681-1692.
42. Wilson BA. Neuropsychological rehabilitation. *Annu Rev Clin Psychol* 2008; 4: 141-162.
43. Wilson BA. Towards a comprehensive model of cognitive rehabilitation. *Neuropsychol Rehabil* 2002; 12: 97-110.
44. Cobo E, Cortés J, Ribera J, et al. Effect of using reporting guidelines during peer review on quality of final manuscripts submitted to a biomedical journal: masked randomised trial. *BMJ* 2011; 343 (Accessed 28 October 2016).

45. Smith BA, Lee H-J, Lee JH, et al. Quality of reporting randomized controlled trials (RCTs) in the nursing literature: application of the consolidated standards of reporting trials (CONSORT). *Nurs Outlook* 2008; 56: 31-37.
46. Plint AC, Moher D, Morrison A, et al. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. *Med J Aust* 2006; 185: 263-267.
47. Kane RL, Wang J and Garrard J. Reporting in randomized clinical trials improved after adoption of the CONSORT statement. *J Clin Epidemiol* 2007; 60: 241-249.
48. Sohlberg MM and Mateer CA. *Cognitive rehabilitation: An integrative neuropsychological approach*. 1st ed. USA: The Guilford Press, 2001.
49. Moher D, Schulz KF, Simera I and Altman DG. Guidance for developers of health research reporting guidelines. *PLoS Medicine* 2010; 7: e1000217 (Accessed 24 August 2016).
50. Mateer CA. Fundamentals of cognitive rehabilitation. In: Halligan PW and Wade DT, (eds.). *Effectiveness of Rehabilitation for Cognitive Deficits*. USA: Oxford University Press, 2005, p. 21-9.
51. Campbell J, Langdon D, Cercignani M and Rashid W. A Randomised controlled trial of efficacy of cognitive rehabilitation in multiple sclerosis: A cognitive, behavioural, and MRI study. *Neural Plasticity*. 2016; 2016: no pagination.
52. Perez-Martin MY, Gonzalez-Platas M, Eguia-Del Rio P, Croissier-Elias C and Sosa AJ. Efficacy of a short cognitive training program in patients with multiple sclerosis. *Neuropsychiatr Dis Treat* 2017; 13: 245-52.
53. Allen DN, Goldstein G, Heyman RA and Rondinelli T. Teaching memory strategies to persons with multiple sclerosis. *J Rehabil Res Dev* 1998; 35: 405-410.
54. Altun GI, Kirbas D, Altun DU, et al. The effects of cognitive rehabilitation on relapsing remitting multiple sclerosis patients. *Noropsikiyatri Arsivi / Archives of Neuropsychiatry* 2015; 52: 174-179.
55. Amato MP, Goretti B, Viterbo RG, et al. Computer-assisted rehabilitation of attention in patients with multiple sclerosis: results of a randomized, double-blind trial. *Mult Scler* 2014; 20: 91-98.
56. Birnboim S and Miller A. Cognitive Rehabilitation for Multiple Sclerosis Patients With Executive Dysfunction. *J Cognit Rehabil* 2004; 22: 11-18.
57. Bonavita S, Sacco R, Della Corte M, et al. Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: an exploratory study. *J Neurol* 2015; 262: 91-100.
58. Brenk A, Laun K and Haase CG. Short-term cognitive training improves mental efficiency and mood in patients with multiple sclerosis. *Eur Neurol* 2008; 60: 304-309.

59. Cerasa A, Gioia MC, Valentino P, et al. Computer-assisted cognitive rehabilitation of attention deficits for multiple sclerosis: a randomized trial with fMRI correlates. *Neurorehabil Neural Repair* 2013; 27: 284-295.
60. Charvet LE, Shaw MT, Haider L, Melville P and Krupp LB. Remotely-delivered cognitive remediation in multiple sclerosis (MS): protocol and results from a pilot study. Mult Scler J Exp Transl Clin 2015; 1: 1-10.
61. Chiaravalloti ND and DeLuca J. The influence of cognitive dysfunction on benefit from learning and memory rehabilitation in MS: A sub-analysis of the MEMREHAB trial. *Mult Scler* 2015; 21: 1575-1582.
62. De Giglio L, De Luca F, Prosperini L, et al. A low-cost cognitive rehabilitation with a commercial video game improves sustained attention and executive functions in multiple sclerosis: A pilot study. *Neurorehabil Neural Repair* 2015; 29: 453-461.
63. De Giglio L, Tona F, De Luca F, et al. Multiple Sclerosis: Changes in Thalamic Resting-State Functional Connectivity Induced by a Home-based Cognitive Rehabilitation Program. *Radiology* 2016; 280: 202-211.
64. Dobryakova E, Wylie GR, DeLuca J and Chiaravalloti ND. A pilot study examining functional brain activity 6 months after memory retraining in MS: the MEMREHAB trial. *Brain Imaging Behav* 2014; 8: 403-406.
65. Ernst A, Botzung A, Gounot D, et al. Induced brain plasticity after a facilitation programme for autobiographical memory in multiple sclerosis: a preliminary study. *Mult Scler Int* 2012; 2012: 820240.
66. Ernst A, Blanc F, Voltzenlogel V, de Seze J, Chauvin B and Manning L. Autobiographical memory in multiple sclerosis patients: assessment and cognitive facilitation. *Neuropsychol Rehabil*2013; 23: 161-181.
67. Filippi M, Riccitelli G, Mattioli F, et al. Multiple sclerosis: effects of cognitive rehabilitation on structural and functional MR imaging measures--an explorative study. *Radiology* 2012; 262: 932-940.
68. Fink F, Rischkau E, Butt M, Klein J, Eling P and Hildebrandt H. Efficacy of an executive function intervention programme in MS: a placebo-controlled and pseudo-randomized trial. *Mult Scler* 2010; 16: 1148-1151.
69. Gentry T. PDAs as cognitive aids for people with multiple sclerosis. *The American journal of occupational therapy : Official publication of the American Occupational Therapy Association* 2008; 62: 18-27.

70. Gich J, Freixanet J, Garcia R, et al. A randomized, controlled, single-blind, 6-month pilot study to evaluate the efficacy of MS-Line!: a cognitive rehabilitation programme for patients with multiple sclerosis. *Mult Scler* 2015; 21: 1332-1343.
71. Janssen A, Boster A, Lee H, Patterson B and Prakash RS. The effects of video-game training on broad cognitive transfer in multiple sclerosis: A pilot randomized controlled trial. *J Clin Exp* Neuropsychol 2015; 37: 285-302.
72. Lincoln NB, Dent A, Harding J, et al. Evaluation of cognitive assessment and cognitive intervention for people with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2002; 72: 93-98.
73. Mantynen A, Rosti-Otajarvi E, Koivisto K, Lilja A, Huhtala H and Hamalainen P. Neuropsychological rehabilitation does not improve cognitive performance but reduces perceived cognitive deficits in patients with multiple sclerosis: a randomised, controlled, multi-centre trial. *Mult Scler* 2014; 20: 99-107.
74. Mattioli F, Stampatori C, Scarpazza C, Parrinello G and Capra R. Persistence of the effects of attention and executive functions intensive rehabilitation in relapsing remitting multiple sclerosis. *Mult Scler Relat Disord* 2012; 1: 168-73.
75. Mendozzi L, Pugnetti L, Motta A, Barbieri E, Gambini A and Cazzullo CL. Computer-assisted memory retraining of patients with multiple sclerosis. *Ital J Neurol Sci* 1998; 19: S431-S8.
76. Pedulla L, Brichetto G, Tacchino A, et al. Adaptive vs. non-adaptive cognitive training by means of a personalized App: a randomized trial in people with multiple sclerosis. *Journal of NeuroEng. Rehabil* 2016; 13: 88.
77. Plohmann A, Kappos L and Brunnschweiler H. Evaluation of a computer-based attention retraining program for patients with multiple sclerosis. *Schweiz Arch Neurol Psychiatr* 1994; 145: 35-36.
78. Plohmann AM, Kappos L, Ammann W, et al. Computer assisted retraining of attentional impairments in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1998; 64: 455-462.
79. Pusswald G, Mildner C, Zebenholzer K, Auff E and Lehrner J. A neuropsychological rehabilitation program for patients with Multiple Sclerosis based on the model of the ICF. *NeuroRehabilitation* 2014; 35: 519-27.
80. Rosti-Otajärvi EM, Mäntynen A, Koivisto K, Huhtala H and Hämäläinen P. Neuropsychological rehabilitation has beneficial effects on perceived cognitive deficits in multiple sclerosis during nine-month follow-up. *J Neurol Sci* 2013; 334: 154-60.

81. Rosti-Otajarvi E, Mantynen A, Koivisto K, Huhtala H and Hamalainen P. Patient-related factors may affect the outcome of neuropsychological rehabilitation in multiple sclerosis. *J Neurol Sci* 2013; 334: 106-11.
82. Sastre-Garriga J, Alonso J, Renom M, et al. A functional magnetic resonance proof of concept pilot trial of cognitive rehabilitation in multiple sclerosis. *Mult Scler* 2011; 17: 457-67.
83. Shatil E, Metzer A, Horvitz O and Miller A. Home-based personalized cognitive training in MS patients: a study of adherence and cognitive performance. *NeuroRehabilitation* 2010; 26: 143-53.
84. Shevil E and Finlayson M. Pilot study of a cognitive intervention program for persons with multiple sclerosis. *Health Education Research*. 2010; 25: 41-53.
85. Tesar N, Bandion K and Baumhackl U. Efficacy of a neuropsychological training programme for patients with multiple sclerosis -- a randomised controlled trial. *Wiener klinische Wochenschrift*. 2005; 117: 747-54.

Figures and Tables

Figure 1. PRISMA Flowchart of Systematic Review Search Results

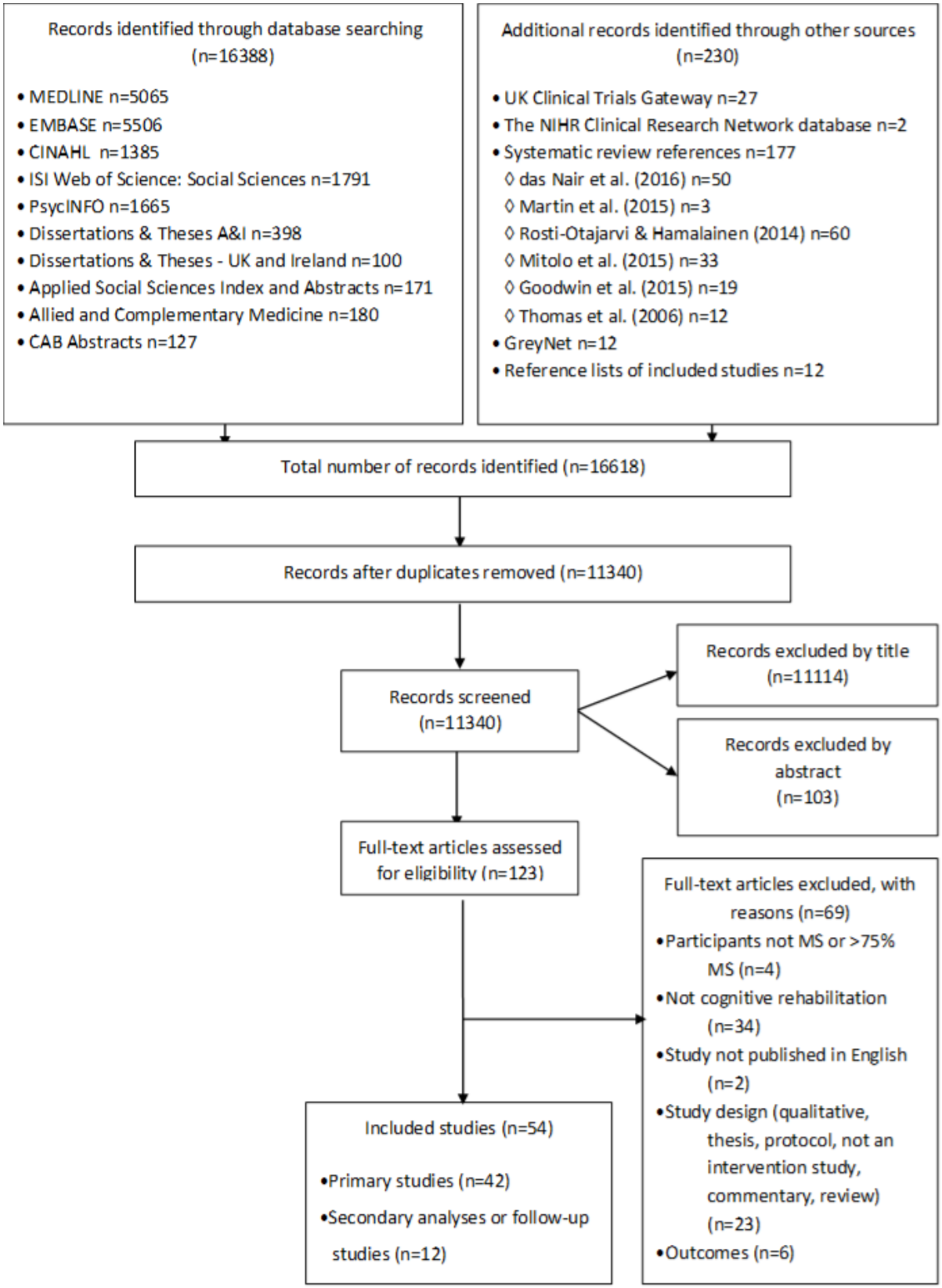


Table 1. Characteristics of included studies by delivery mode and cognitive domain targeted in the intervention

Cognitive Domain	**Delivery Mode**		
	Individual	Group	Blended
Memory only	Allen (1998)[43], Ernst (2012)[32], Ernst (2013)[31], Gentry (2008)[51], Pedulla (2016)[59], Vogt (2009)[66]	Carr (2014)[1], Chiaravalloti (2012)[28]	Martin (2014)[68]
Attention only	Amato (2014)[24], Cerasa (2013)[27], Plohmann (1994)[60], Plohmann (1998)[61], Rosti-Otajarvi (2013)[40]	-	-
Executive function only	Birnboim and Miller (2004)[44], Fink (2010)[33]	-	Hanssen (2015)[54]
Combination	Altun (2015)[23], Bonavita (2015)[25], Brenk (2008)[45], Charvet (2015)[22], Campbell (2016)[51], De Giglio (2015)[29], De Giglio (2016)[30], Ernst (2015)[21], Filippi (2012)[20], Gich (2015)[52], Hancock (2015)[53], Hildebrandt (2007)[3], Janssen (2015)[34], Jonsson (1993)[55], Lincoln (2002)[57], Mantynen (2014)[35], Mattioli (2010)[36], Mattioli (2012)[37], Mattioli (2014)[38]; Mattioli (2016)[39]; Mendozzi (1998)[58]; Parisi (2014)[46], Perez-Martin (2007)[52], Rosti-Otajarvi (2013)[41], Sastre-Garriga (2011)[63], Shatil (2010)[6], Solari (2004)[4]	Brissart (2013)[26], Chiaravalloti (2005)[47], Chiaravalloti (2013)[48], Chiaravalloti and DeLuca (2015)[49], Dobryakova (2014)[50], Leavitt (2014)[56], Shevil and Finlayson (2010)[42], Tesar (2005)[65]	Pusswald (2014)[62], Stuifbergen (2012)[2]

Table 2. A summary of the reporting quality of the 54 included studies for selected reporting items

Broad aspect of reporting	No. (%) of studies in which item was reported completely*	No. (%) of studies in which item was not clearly reported*	No. (%) of studies in which item was not reported	No. (%) of studies in which item was not applicable**
Demographic and clinical characteristics of the participants	51 (94%)	0	3 (6%)	n/a
Theory/conceptual framework upon which the intervention is based	29 (54%)	21 (39%)	4 (7%)	n/a
Key elements of intervention, including active ingredients and mechanism of action	21 (39%)	29 (54%)	4 (7%)	n/a
Details of the intervention content i.e., what participants received	26 (48%)	24 (44%)	4 (7%)	n/a
Specific details about the procedures	16 (30%)	36 (66%)	2 (4%)	n/a
Level of professional training of the person who delivered the intervention	6 (11%)	13 (24%)	4 (7%)	31 (57%)**
Number of people who delivered the intervention	5 (9%)	3 (6%)	15 (27%)	31 (57%)**
Individual delivering intervention received training specific to the intervention	0	4 (7%)	19 (35%)	31 (57%)**
Competency to deliver intervention assessed and achieved	3 (7%)	10 (18%)	10 (18%)	31 (57%)**

Broad aspect of reporting	No. (%) of studies in which item was reported completely*	No. (%) of studies in which item was not clearly reported*	No. (%) of studies in which item was not reported	No. (%) of studies in which item was not applicable**
Delivery mode: Individual or group	24 (44%)	8 (15%)	22 (41%)	n/a
The intervention 'dose': intended and actual	17 (31%)	35 (65%)	2 (4%)	n/a
Materials	12 (22%)	32 (59%)	10 (19%)	n/a
Assessment of fidelity (specifically referring to delivery of the intervention by the facilitator, therapist, etc.)	3 (13%)	8 (15%)	14 (27%)	31 (57%)**
Adherence/compliance of participants to intervention	9 (17%)	6 (12%)	37 (71%)	n/a

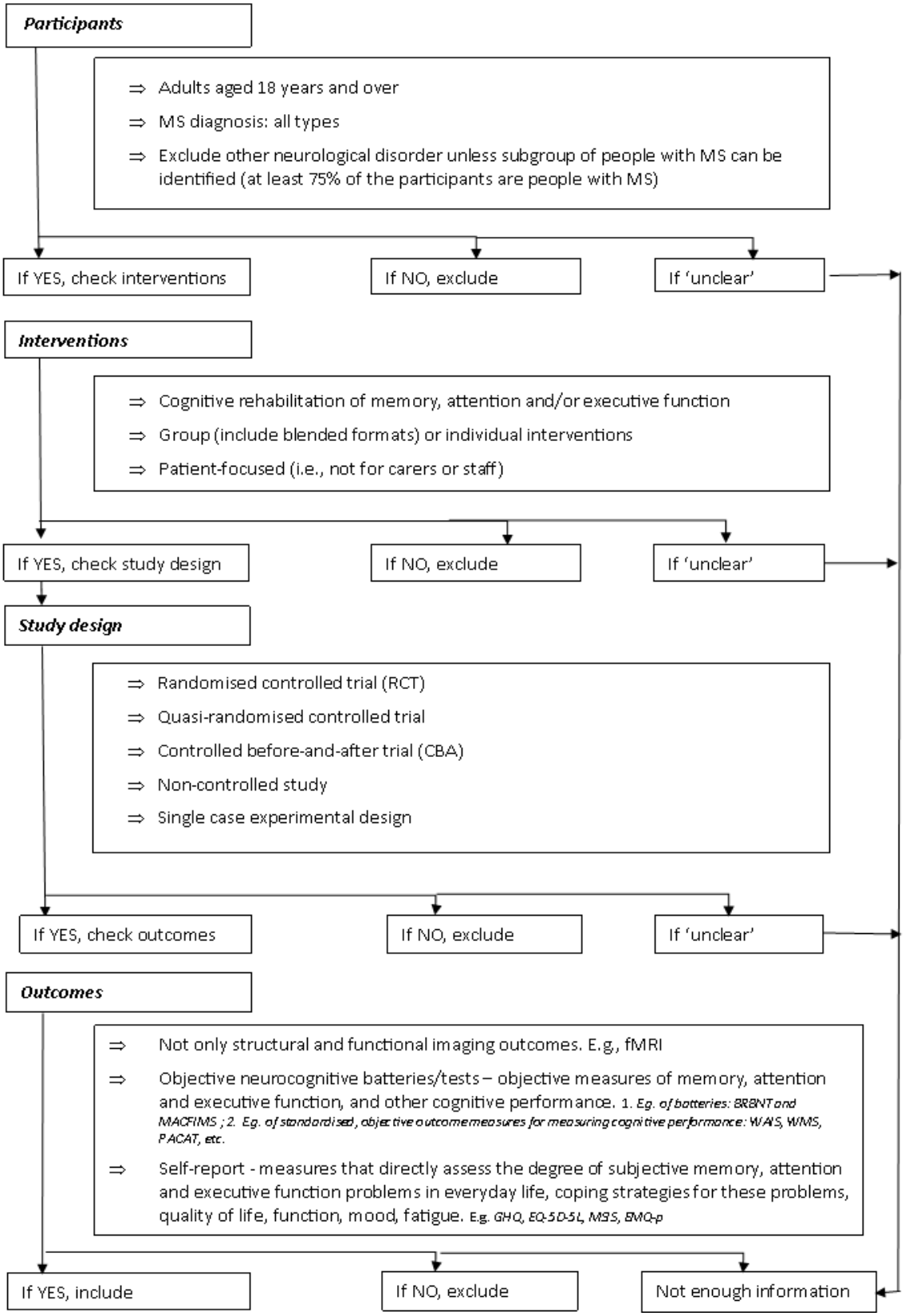
Note: *Assessed against the description of the reporting item for the checklists used; **not applicable for computer-based interventions.

Supplementary data

Supplementary Data File 1. MEDLINE In-Process & Other Non-Indexed Citations (Ovid) search strategy

1. exp Multiple Sclerosis/
2. exp demyelinating autoimmune diseases, cns/
3. "autoimmune diseases of the nervous system"/
4. multiple sclerosis.ab,ti.
5. 1 or 2 or 3 or 4
6. exp *Cognition Disorders/ or exp *Cognition/
7. exp *Cognitive Dissonance/
8. exp *Mild Cognitive Impairment/
9. exp *Metacognition/
10. exp *Awareness/
11. exp *Attention/
12. exp *Memory/ or exp *Memory Disorders/
13. mental processes/ or exp *executive function/
14. (cogniti* or neuropsychol* or memor* or attenti* or execut* or metacognit* or aware* or concentrat*).ab,ti.
15. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 5 and 15
17. exp *Neurological Rehabilitation/ or exp *Rehabilitation/ or exp *Rehabilitation Research/
18. exp *Cognitive Therapy/
19. exp *Neuropsychology/
20. exp Therapy, Computer-Assisted/
21. exp Computers/
22. exp Neuropsychological Tests/
23. (interven* or train* or re?train* or computer?assisted therap* or rehabilit* or neurorehab* or neuropsych* rehab* or restitut* or remediat* or restorat* or retrain* or train* or recover* or treat* or guid* or instruct* or teach* or stimulat* or exerci* or strateg* or counsel* or therap* or intervent* or manage*).ab,ti.
24. 17 or 18 or 19 or 20 or 21 or 22 or 23
25. (attent* or memor* or cognit* or cogniti* disorder* or concentrat* or awar* or alert* or distract* or executive function).ab,ti.
26. 24 and 25
27. 16 and 26

Supplementary Data File 2. Hierarchy for Excluding Studies



Supplementary Data File 3. Characteristics of Included studies

First author, year published	Study design	Type of multiple sclerosis (RRMS – relapsing remitting MS; PPMS – primary progressive MS; SPMS – secondary progressive MS; chronic progressive – CPMS; progressing relapsing - PRMS	Cognitive domain	Age of participants	Format of intervention delivery	Intervention technique	Study status – 1: primary study; 2: secondary/sub-group analyses; 3: follow-up study
Allen, 1998[53]	Before and after	Non-specific MS	Memory	39.6 (8.71)	Individual, computer-based	Computer-based imagery-based mnemonic strategy training	1
Altun,2015[54]	Before and after	RRMS	Attention, sustainable attention, information processing speed, and verbal and visual memory	36 (7.19)	Individual, Computer-based	Different screens used, based on cognitive domains. For example, memory screen had tasks such as identification of objects and deduction exercises.	1
Amato, 2014[55]	RCT	RRMS	Attention	18–55 years (inclusion criteria)	Individual, home-based, computer-based	Based on the Attention Processing Training program (APT). Focus is on restorative exercises	1
Birnboim, 2004[56]	Before and after	Non-specific MS	Executive function	45.5 (9.25)	Individual, computer-based	Strategy training, awareness and learning application to daily life. Computer-based	1
Bonavita, 2015[57]	CBA	RRMS	Attention and information processing speed	49 (8)	Individual, computer-based	Short-term cognitive training based on Reckon	1
Brenk, 2008[58]	CBA	Non-specific MS	Non-specific, but targets memory and attention	43.5(8.9)	Individual	Non-specific cognitive training (restitution)	1
Brissart, 2013[25]	CBA	RRMS	Memory and executive function	42.5 (5.17);	Group	Group proctor-SEP Cognitive Program - aims to teach the patient to use facilitation strategies to help preserved functions	1
Campbell, 2016[51]	RCT	RRMS, SPMS	Working memory, visuospatial memory, divided attention	47.37 (8.23)	Individual	Restitution. Cognitive training to improve/increase brain activation of specific brain areas and thus improve neural efficiency	1
Carr, 2014[1]	RCT	PPMS, SPMS, RRMS, benign	Memory	34-72	Group	Group memory rehabilitation programme combining restitution and compensation strategies	1
Cerasa, 2013[59]	RCT	RRMS	Attention	31 (9.2)	Individual, home based, computer-assisted	Software reckon -computer-based intensive attention training program	1
Charvet, 2015[60]	RCT	RRMS	Working memory and processing speed	19-55 years	Individual	Computer-based, active adaptive cognitive remediation program focusing on training common areas of impairment in multiple sclerosis	1

Supplementary Data File 3. Characteristics of Included studies

First author, year published	Study design	Type of multiple sclerosis (RRMS – relapsing remitting MS; PPMS – primary progressive MS; SPMS – secondary progressive MS; chronic progressive – CPMS; progressing relapsing - PRMS	Cognitive domain	Age of participants	Format of intervention delivery	Intervention technique	Study status – 1: primary study; 2: secondary/sub-group analyses; 3: follow-up study
Chiaravalloti, 2005[30]	RCT	RRMS, PPMS and SPMS	Memory and learning	45.14 (13.78)	Group	Story Memory Technique (mSMT) focusing on approving the acquisition of info through context and imagery) into long-term memory	1
Chiaravalloti, 2012[31]	RCT	RRMS	Memory	49.25 (9.33)	Group	Engagement of imagery procedures to facilitate learning + use of context to organize incoming information	2
Chiaravalloti, 2013[24]	RCT	RRMS, PPMS, SPMS, PRMS	Memory and learning	Inclusion criteria; age 30–70 year. I: 48.13 (10.17);	Group	Modified Story Memory Technique (mgmt.) focusing on approving the acquisition of info through context and imagery) into long-term memory	Similar studies as Chiaravalloti 2012, Dobryakova 2014 and Leavitt 2012
Chiaravalloti, 2015[61]	RCT	RRMS, PPMS, SPMS, PRMS	Memory and learning	48.13 (10.17)	Group	Modified Story Memory Technique (mSMT) focusing on approving the acquisition of info through context and imagery) into long-term memory	2: Post-hoc analysis of Chiaravalloti et al., 2013
De Giglio, 2015[62]	RCT (waiting list control)	RRMS	Attention, working memory, processing speed and executive function	43.9 (8.4)	Individual, home-based, computer	Computer and videogame-based training	1
De Giglio, 2016[63]	RCT (waiting list control)	RRMS	Attention, working memory, processing speed and executive function	43.2 (8.2)	Individual, home-based, computer	Computer and videogame-based training	2: Further analyses of De Giglio 2015
Dobryakova, 2014[64]	RCT	RRMS and PPMS	Memory and learning	40 (5.66)	Group	Modified Story Memory Technique (mSMT) focusing on approving the acquisition of info through context and imagery) into long-term memory	3: Follow-up of Chiaravalloti (2013)
Ernst, 2012[65]	CBA	RRMS	Autobiographical memory	37.25 (5.5)	Individual	Mental visual imagery (MVI)-based exercises - compensatory	1

Supplementary Data File 3. Characteristics of Included studies

First author, year published	Study design	Type of multiple sclerosis (RRMS – relapsing remitting MS; PPMS – primary progressive MS; SPMS – secondary progressive MS; chronic progressive – CPMS; progressing relapsing - PRMS	Cognitive domain	Age of participants	Format of intervention delivery	Intervention technique	Study status – 1: primary study; 2: secondary/sub-group analyses; 3: follow-up study
Ernst, 2013[66]	CBA	RRMS	Autobiographical memory	42.96 (10.94);	Individual	An MVI (mental visual imagery)-based cognitive facilitation programme - compensatory	1
Ernst, 2015[35]	RCT	RRMS	Executive function, autobiographical memory	42 (10.37)	Individual	Mental visual imagery (MVI)-based exercises	1
Filippi, 2012[67]	RCT	RRMS	Attention and information processing and executive functions	44.8 (28-60);	Individual, computer-based	Domain-specific cognitive training. Computer software – reckon package	1
Fink, 2010[68]	CBA	RRMS	Executive function	44.8 (8.2)	Individual	Ease executive deficits by self-training and receiving feedback	1
Gentry, 2008[69]	Before and after	RRMS, PPMS, SPMS, CPMS	Memory	50 (37-73)	Individual, home based	PDA; compensatory assistive technology/strategy	1
Gich, 2015[70]	RCT	RRMS and SPMS	Memory and executive function	45.5 (9.6)	Individual, computer-based	Cognitive rehabilitation programme based on the restoration of function	1
Hancock, 2015[26]	RCT	RRMS, SPMS, PPMS	Processing speed and working memory	50.65 (6.32)	Individual, home-based, computer-based	Computerized cognitive training (Posit Science)	1
Hanssen, 2015[33]	RCT	PPMS, RRMS, SPMS	Executive function	53.9 (33-70)	Blended	Goal attainment. Psychoeducation, learning strategies	1
Hildebrandt, 2007[3]	RCT	RRMS	Memory and working memory	42 (25-55)	Individual, home-based, computer-based	Home-based cognitive training program, designed to increase frequency and intensity of training	1
Janssen, 2015[71]	RCT (waiting list control)	RRMS	Attention, working memory, executive functioning and processing speed	30-59 (inclusion criteria); I=49.4396.4), C=44.96(8.8)	Individual	Cognitive training through multimodal videogame-based learning strategies: Hybrid-variable priority training (HVT) program	1
Jonsson, 1993[34]	RCT	RRMS, secondary CPMS and primary CPMS course	Memory and attention (concentration)	46.1 (7.3);	Individual	Compensation (internal and external memory aids), substitution, direct training (puzzles, etc.) + neuropsychotherapy.	1

Supplementary Data File 3. Characteristics of Included studies

First author, year published	Study design	Type of multiple sclerosis (RRMS – relapsing remitting MS; PPMS – primary progressive MS; SPMS – secondary progressive MS; chronic progressive – CPMS; progressing relapsing - PRMS	Cognitive domain	Age of participants	Format of intervention delivery	Intervention technique	Study status – 1: primary study; 2: secondary/sub-group analyses; 3: follow-up study
Leavitt, 2014[32]	RCT	RRMS, PPMS, SPMS, PRMS	Memory and learning	49.72 (9.98)	Group	Modified Story Memory Technique (mSMT)) focusing on approving the acquisition of info through context and imagery) into long-term memory	2: Sub-group analysis of Chiaravalloti 2012
Lincoln, 2002[72]	RCT	SPMS, RRMS, including benign, PPMS	Range of cognitive deficits (dependent of participants' needs), including memory	43 (10)	Individual	Identification of individual needs. Compensatory techniques includes training in use of external memory aids (diaries, calendars, note books) + internal memory aids (visual mnemonics)	1
Mantynen, 2014[73]	RCT	RRMS	Attention and working memory	Inclusion criteria age range 18-58. 43.5 (8.7);	Individual, computer-based	Strategy-oriented computer-based attention and working memory retraining, psychoeducation and teaching compensatory strategies	1
Martin, 2014[13]	RCT	Not stated	Memory	45.2-48.3	Blended: 2 individual sessions and 10 group sessions	Compensatory (external memory aids) or restitution (encoding and retrieval practice, and attention- retraining exercises e.g. Letter and number cancellation	2
Mattioli, 2010[28]	RCT	RRMS	Attention, information processing, executive function	42 (41-53)	Individual, computer-based	RehaCom computer-based intensive training	1
Mattioli, 2012[74]	RCT	RRMS	Attention, information processing and executive function	45.46(10.48)	Individual, computer-based	Intensive neuropsychological training	1
Mattioli, 2014[27]	RCT	RRMS	Attention/speeded information, executive function and memory	45 (38-50)	Individual, computer-based	Domain-specific cognitive training (based on individual cognitive impairment)	3: Follow-up 1 of Mattioli (2010)
Mattioli, 2016[29]	RCT	RRMS	Memory, attention/speeded information processing and executive function	44.8 (8.69)	Individual, computer-based	Domain-specific cognitive training (based on individual cognitive impairment)	3: Two year follow-up of Mattioli et al (2010)
Mendozzi, 1998[75]	Quasi-RCT	RRMS or secondary CPMS	Memory and attention	45.38-47.92	Individual, computer-based	Memory training (encoding) and attention tasks	1

Supplementary Data File 3. Characteristics of Included studies

First author, year published	Study design	Type of multiple sclerosis (RRMS – relapsing remitting MS; PPMS – primary progressive MS; SPMS – secondary progressive MS; chronic progressive – CPMS; progressing relapsing - PRMS	Cognitive domain	Age of participants	Format of intervention delivery	Intervention technique	Study status – 1: primary study; 2: secondary/sub-group analyses; 3: follow-up study
Parisi, 2014[36]	RCT	Non-specific MS	Attention, information processing and executive function	43.6 (25-58)	Individual, computer-based	Domain-specific cognitive training. Computer software – reckon package	3: Follow-up of Mattioli et al (2010)
Pedulla, 2016[76]	RCT	RRMS, SPMS	Working memory	47.5 (9.3)	Individual, home-based, computer	Computer-based adaptive cognitive training	1
Plohmann, 1994[77]	CBA (waiting list control)	RRMS, CPMS	Attention	39.7 (10.09)	Individual, computer-based	Retraining, restitution	1
Perez-Martin, 2017[52]	RCT	RRMS, PPMS, SPMS	Memory, attention, processing speed and executive function	44.93 (9.89)	Individual, home-based, computer-based	Multi-domain computer-assisted cognitive rehabilitation supported by home-based work	1
Plohmann, 1998[78]	SCED	Primary CPMS, Secondary CPMS, RRMS	Attention	44.6 (11.4)	Individual, computer-based	Four attention training programme; focus on two of most affected/diminished attention areas - specific + nonspecific training	1
Pusswald, 2014[79]	RCT	RRMS, SPMS, PPMS	Divided attention. Cog rehab included memory retraining	42.6 (1)	Blended: Individual (home-based computer training) and group psychosocial counselling	Cognitive functional training + psychosocial counselling focusing on restitution training and compensation strategies	1
Rosti-Otajarvi, 2013a[80]	RCT	RRMS	Attention	43.5 (8.7);	Individual, computer-based	Strategy-oriented computer-based attention and working memory retraining, psychoeducation and teaching compensatory strategies	2: Secondary paper to Mantynen 2014
Rosti-Otajärvi, 2013b[81]	RCT	RRMS	Attention and working memory	18–59	Individual	Strategy-oriented computer-based attention and working memory retraining, psychoeducation and teaching compensatory strategies	3: Follow-up to Mantynen 2014
Sastre-Garriga, 2011[82]	CBA	RRMS, PPMS, SPMS	Attention, executive function and memory	50.73 (10.88)	Individual, computer-based	Intervention targeted worse affected cognitive domain. Training	1

Supplementary Data File 3. Characteristics of Included studies

First author, year published	Study design	Type of multiple sclerosis (RRMS – relapsing remitting MS; PPMS – primary progressive MS; SPMS – secondary progressive MS; chronic progressive – CPMS; progressing relapsing - PRMS	Cognitive domain	Age of participants	Format of intervention delivery	Intervention technique	Study status – 1: primary study; 2: secondary/sub-group analyses; 3: follow-up study
Shatil, 2010[83]	CBA	RRMS and PRMS	Non-specific: it is composed of 15 evaluation tasks measuring a wide range of cognitive abilities such as memory, attention and eye-hand coordination	43.75 (12.15)	Individual, computer-based, home-based	CogniFit Personal Coach (CPC), a home-based, computerized, individualized cognitive training program	1
Shevil, 2010[84]	Before and after	Non-specific MS	Memory, attention, information processing and executive function	52.4 (10.3); range 26-70	Group	Internal and external compensatory strategies (e.g. mnemonics, incorporating a day planner or digital recorder and organizing spaces).	1
Solari, 2004[4]	RCT	RRMS, PRMS, CPMS	Memory and attention	46.2 (9.2)	Individual, computer-based	Rehacom ; computer-based memory and attention retraining	1
Stuifbergen 2012[2]	RCT	Non-specific MS	Attention, Memory, Problem solving, executive skills	24-60; 47.95 (8.76)	Blended	MAPSS-MS : group sessions focusing on compensatory strategies + individual-based computer-assisted cognitive training program	1
Tesar, 2005[85]	RCT	RRMS and SPMS	Memory and learning	45.3 (9.2)	Group, computer-based	Direct functional training + teaching of compensation strategies relevant to everyday life	1
Vogt, 2009[37]	Quasi-RCT	RRMS, SPMS and CPMS	Working memory	43.2 (8.8);	Home-based, individual	High intensity, computer-based, working memory training - BrainStim	1

Supplementary Data File 4. Data extraction of the content of the interventions of the included studies

Information is reported completely, as per item description	
Information is reported incompletely, as per item description	
Information is not reported	
Reporting item not applicable	n/a

	Allen 1998[53]	Altun 2015[54]	Amato 2014[55]	Birnboim 2004[56]	Bonavita 2015[57]	Brenk 2008[58]	Brissart 2013[25]	Campbell, 2016[51]	Carr 2014[1]	Cerasa 2013[59]	Charvet 2015[60]	Chiaravalloti 2005[30]	Chiaravalloti 2012[31]	Chiaravalloti 2013[24]	Chiaravalloti 2015[61]	De Giglio 2015[62]	De Giglio 2016[63]	Dobryakova 2014[64]	Ernst 2012[65]	Ernst 2013[66]	Ernst 2015[35]	Filippi 2012[67]	Fink 2010[68]	Gentry 2008[69]	Gich 2015[70]	Hancock 2015[26]	Hanssen 2015[33]	Hildebrandt 2007[3]	Janssen 2015[71]	Jonsson 1993[34]	Leavitt 2014[32]	Lincoln 2002[72]	Mantynen 2014[73]	Martin 2014[13]	Mattioli 2010[28]	Mattioli 2012[74]	Mattioli 2014[27]	Mattioli 2016[29]	Mendozzi 1998[75]	Parisi 2014[36]	Pedulla 2016[76]	Perez-Martin,	Plohmann 1994[77]	Plohmann 1998[78]	Pusswald 2014[79]	Rosti-Otajarvi	Rosti-Otajärvi	Sastre-Garriga	Shatil 2010[83]	Shevil 2010[84]	Solari 2004[4]	Stuifbergen 2012[2]	Tesar 2005[85]	Vogt 2009[37]
Demographic and clinical characteristics of the participants																																																						
Theory/conceptual framework upon which the intervention is based																																																						
Key elements of intervention, including active ingredients and mechanism of action																																																						
Details of the intervention content i.e., what participants received																																																						
Specific details about the procedures																																																						
Level of professional training of the person who delivered the intervention	n/a	n/a	n/a	n/a	n/a			n/a		n/a	n/a					n/a	n/a					n/a			n/a	n/a		n/a					n/a		n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a		n/a		n/a	n/a		n/a		n/a	n/a
Number of people who delivered the intervention	n/a	n/a	n/a	n/a	n/a			n/a		n/a	n/a					n/a	n/a					n/a			n/a	n/a		n/a					n/a		n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a		n/a		n/a	n/a		n/a		n/a	n/a
Individual delivering intervention received training specific to the intervention	n/a	n/a	n/a	n/a	n/a			n/a		n/a	n/a					n/a	n/a					n/a			n/a	n/a		n/a					n/a		n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a		n/a		n/a	n/a		n/a		n/a	n/a
Competency to deliver intervention assessed and achieved	n/a	n/a	n/a	n/a	n/a			n/a		n/a	n/a					n/a	n/a									n/a	n/a	n/a					n/a		n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a		n/a	n/a		n/a		n/a	n/a
Delivery mode: Individual or group																																																						
The intervention ‘dose’: intended and actual																																																						
Materials																																																						
Assessment of fidelity																																																						
Adherence/compliance of participants to intervention																																																						