Sys Rev Pharm 2020;11(11):1252-1262
A multifaceted review journal in the field of pharmacy

Protocol for a Systematic Review and Meta-Analysis on Randomized Clinical Trials on the Efficacy and Safety of Sphingosine-1-Phosphotase Receptor Modulators

Asim Ahmed Elnour[1], Adel Sadeq[2], Farah Hamad Farah[3], Noor Alhouda Kassem[4], Haia Abdulsamad[5], N Al Mazrouei[6], Israa Yousif Khidir[7], Doaa Nassar[8], Abubakar B. Abubakar[9], Abdelgadir Elamin[10], Abdulla Al Amoodi[11], Sasha Mohammed Elamin Suliman[12], Mohamed Elamin Hassan[13], Noora Alhajri[14], Ekrima Elmoeiz Gaffar Osman[15], Salma Mohamed Magboul[16], Judit Don[17]; Jamila Alaryani[18], Islam Moahmmed Abd Alla[19], Warda Salah Mohammed Elkhalifa[20], Nadeen T Ali[21], Hanan Siddig Ali Alamin[22], Hagar Awad Abdelrahim[23], Sahar Asim Ahmed Elnour[24], Asil Adel[25], Wadah Mohamed Ali Khogali[26], Haya Hamed Ahmed Lulu[27]

[1*]Asim Ahmed Elnour, (PhD, MSc) Associate Professor, College of Pharmacy, Al Ain University, Al Ain-United Arab Emirates (UAE). Email: asim.ahmed@aau.ac.ae, assahura2021@gmail.com; ORCID: https://orcid.org/0000-0002-4143-7810.

[2]Adel Sadeq, (PhD, MSc), Assistant Professor, Program of Clinical Pharmacy, College of Pharmacy, Al Ain University, Al Ain-UAE. Email: adel.sadeq@aau.ac.ae; ORCID https://orcid.org/0000-0001-9529-8898.

[3]Farah Hamad Farah, (PhD), Associate Professor, Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Ajman University, Ajman-UAE. Email: f.hamad@ajman.ac.ae; ORCID https://orcid.org/0000000333399743.

[4]Noor Alhouda Kassem, (B-Pharm), Pharmacist; Abu Dhabi Health Services, Abu Dhabi-UAE. Email: nakassem72@gmail.com, ORCID: https://orcid.org/0000-0002-4225-7870.

[5]Haia Abdulsamad, (B-Pharm), Pharmacist; Abu Dhabi Health Services, Abu Dhabi-UAE. Email: haia_abdulsamad@hotmail.com; ORCID: https://orcid.org/0000-0001-9395-3254.

[6]Nadia Al Mazrouei (Al Mazrouei N), Assistant Professor, Department of Pharmacy Practice and Pharmacotherapeutics, Faculty of Pharmacy, University of Sharjah, United Arab Emirates, Email: nalmazrouei@sharjah.ac.ae.

[7]Israa Yousif El Khidir, (PhD), Clinical Pharmacist, Omdurman Islamic University, Omdurman-Sudan. Email: israamak81@gmail.com; ORCID: https://orcid.org/0000-0001-8674-3603.

[8]Doaa Nassar, (B-Pharm); Pharmacist; Abu Dhabi Health Services, Abu Dhabi-UAE. Email: doaa.nassar000@gmail.com; ORCID: https://orcid.org/0000-0003-0833-1341.

[9]Abubakar B. Abubakar, Lecturer, Department of Medical Imaging and Radiation Sciences, Monash University. Email:abubakar.abubakar@monash.edu, ORCID: https://orcid.org/0000-0002-0922-572x.

[10]Abdelgadir Elamin, (PhD, MSc) Assistant Professor, Medical Laboratory Sciences College of health sciences Gulf Medical University, Ajman-UAE. Email: dr.abdel@gmu.ac.ae; ORCID https://orcid.org/0000-0002-2442-2756.

[11]Abdulla Al Amoodi, Ambulatory Healthcare Services, Academic Affairs, Abu Dhabi Health Services (SEHA), UAE. Email: aalamoodi@seha.ae; ORCID: https://orcid.org/0000-0001-5248-9598.

[12]Sasha Mohammed Elamin Suliman, (PhD-student, MSc), Lecturer, Clinical pharmacy, College of Pharmacy, Riyadh Elm University Riyadh-Saudi Arabia. Email: sashaburass@gmail.com. ORCID: https://orcid.org/0000-0001-.0000-0002-0226-0602

[13]Mohamed Elamin Hassan, (Msc, B Pharm), Clinical Pharmacist, Sheikh Shakhbout
Medical City, Abu Dhabi-UAE. Email: Mohamedelamin5005@gmail.com; ORCID: https://orcid.org/0000-0002-7118-827X.

[14]Noora Alhajri (MD, MPH), Department of Epidemiology and Population Health, Khalifa University, Abu Dhabi-UAE. Email: nalhajri007@gmail.com; ORCID: https://orcid.org/0000-0001-7205-7493.

[15]Ekrima Elmoeiz Gaffar Osman, (MSc, B-Pahrm) Clinical Preceptor, Ibn Sina University, Khartoum-Sudan. Email: ekrimasadan@gmail.com; ORCID: https://orcid.org/0000-0001-5230-0476.

[16]Salma Mohammed Magboul, Pharmacist, (MSc, B Pharm), Marabat Pharmacy, Khartoum, Sudan; Email: salma.magboul2015@gmail.com; ORCID: https://orcid.org/0000-0003-1699-2123

[17]Judit Don, (PharmD student), College of Pharmacy, Gulf Medical University, Ajman-UAE. Email: judited28@gmail.com; ORCID: https://orcid.org/0000-0003-3066-5962.

[18]Jamila Alaryani, Pharmacist, Abu Dhabi Health Services, Abu Dhabi-UAE. Email: jalaryani1828@yahoo.com; ORCID: https://orcid.org/ 0000-0002-3806-8583.

[19]Islam Mohammed Abd Allah, Teaching Assistant, (MSc, B pharm); Faculty of pharmacy, Managel University for Science and Technology, Managel, Sudan. Email: islamsangac@gmail.com; ORCID: https://orcid.org/0000000345132333.

[20]Warda Salah Mohammed Elkhalifa, (Msc, B-Pharm), Clinical Pharmacist. Faculty of Pharmacy, University of Khartoum-Sudan. Email: salahwar83@gmail.com; ORCID: https://orcid.org/0000-0003-1423-3174.

[21]Nadeen T. Ali, (MSc, B-pharm) Clinical Pharmacy Lecturer, Department of Pharmacology, Faculty of Pharmacy, University of Khartoum, Khartoum, Sudan. Email: nadeentajalsir@gmail.com; ORCID: https://orcid.org/0000-0002-5105-5891.

[22]Hanan Siddig Ali Alamin, (MSc, B Pharm), Clinical Pharmacist, Ministry of Health, Aldamer Teaching Hospital, Aldamer-Sudan. Email: hanan4u2@yahoo.com; hananalameen4u2@gmail.com; ORCID: http://orcid.org/0000-0002-6516-4685.

[23]Hagar Awad Abdelrahim, (MSc, B Pharm), Clinical Pharmacist. Independent Researcher. Email: hagarawad1213@gmail.com; hagarawad1413@yahoo.com; ORCID: https://orcid.org/0000-0002-3395-843x.

[24]Sahar Asim Ahmed Elnour, Dentist, MySmile Dental Clinic, Dubai, UAE. Email:al-sahura1995@hotmail.com, ORCID https://orcid.org/0000-0002-6052-5883.

[25]Asil Adel, PhD student; Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin, Republic of Ireland. Email: sadeqa@tcd.ie; ORCID: https://orcid.org/0000-0001-8540-0588.

[26]Wadah Mohamed Ali Khogali, (PhD, MSc), Associate Professor, Medical Imaging Sciences College of Health Sciences, Gulf Medical University, Ajman-UAE. Email**:** dr.wadah@gmu.ac.ae; ORCID**:** 0000-0001-8652-438x.

[27]Haya Hamed Ahmed Lulu, Pharmacist, Bin Sina Pharmacy, Email: haya.h07@hotmail.com; ORCID: https://orcid.org/0000-0002-6114-058X.

Contact person for correspondence
*Asim Ahmed Elnour Ahmed, Clinical Pharmacy Program, College of Pharmacy, Al Ain University, Al Ain-UAE.
Tele: +971551386826 **Email**: assahura2021@gmail.com

ABSTRACT

Background: Sphingosine-1-phosphate (S1P) receptor modulators is a new group that possesses some advantages over the other conventional therapy for multiple sclerosis.
Aim of the review: The aim is to assess the efficacy and safety of sphingosine-1-phosphate receptor modulators.
Methods: The protocol has been developed based on the PRISMA-P checklist by using (PICO [population, intervention, comparators, and outcome]) items, for adult subjects who have received Sphingosine-1-phosphate (S1P) receptor modulators (amiselimod; ozanimod; ponesimod; siponimod) in randomized clinical trials. The subjects with multiple sclerosis (population) receiving sphingosine-1-phosphate receptor modulator (intervention) will be compared to placebo or other modalities of multiple sclerosis (comparators), for the non-inferiority or superiority in terms of effects on walk, disability, relapse and/or other disease clinical markers (outcome). The secondary safety outcomes such as treatment-emergent adverse events and Quality of Life-54 will be assessed as well. The RevMan will be used to quantify the synthesis of data. Whereas I2 index, tau squared, and the Q-test P value will be used to examine heterogeneity among individual trials' effect sizes.
Conclusion: This protocol will report the differences in the efficacy and safety of sphingosine-1-phosphate receptor modulators (intervention) as compared to the placebo or other modalities (comparators).

Keywords: Amiselimod; multiple sclerosis (MS); ozanimod; ponesimod; randomized clinical trials (RCTs), siponimod

Correspondence:
Asim Ahmed Elnour Ahmed
Clinical Pharmacy Program, College of Pharmacy, Al Ain University, Al Ain-UAE.
Email: assahura2021@gmail.com; asim.ahmed@aau.ac.ae

Impact of findings on clincial practice

- Sphingosine-1-phosphate receptor modulators might have better benefit-risk profile that provides option for management of multiple sclerosis.
- Sphingosine-1-phosphate receptor modulators might be clinically effective in short and long-term for multiple sclerosis relapses, magnetic resonance imaging lesions, and disability progression.
- Sphingosine-1-phosphate receptor modulators might provide better safety profile with improved patient's satisfaction with transient and rare serious adverse events.
- Sphingosine-1-phosphate receptor modulators may permit clinicians to make informed decisions about the most efficacious and safest regimen for their clients.
- Sphingosine-1-phosphate receptor modulators may permit clinicians to enforce evidence-based clinical practices and add to the gained knowledge of such therapy.

INTRODUCTION

Multiple sclerosis (MS) was first recognized as a condition since early in the 19th century, [1]. There were 2,500,000 people in the world diagnosed with MS, [2]. The proportion of women with MS is increasing, with 2 to 3 women with MS for every man with the condition. There is evidence to suggest that both MS incidence and prevalence rates have increased over the last few decades, [3].

It has been well known that 50.0% or more of individuals with relapsing-remitting multiple sclerosis (RRMS) transition to secondary progressive multiple sclerosis (SPMS) within 15–20 years, [4].

Therefore, therapy targeting RRMS is of paramount importance. The new members of sphingosine-1-phosphate (S1P) receptor modulators (amiselimod, ozanimod, ponesimod, siponimod) may offer advantage over conventional therapy for RRMS and may provide great opportunity to improve patients' disability, advance control of SPMS and prevent further progression.

The Food and Drug Administration (FDA) approved the first interferon (INF) for treatment of MS in 1993, [5]. However, the use of the INFs remains controversial as these treatments are associated with long-term serious adverse events and their benefit-risk balance might be unfavorable. As new treatment in the field are evolving, INFs are less commonly prescribed as first line treatments, because newer oral and infusion Disease Modifying therapies DMTs are more effective and better tolerated in terms of patient satisfaction and adherence, [6].

Recent study evaluating disability progression in relapse-free MS patients has found that fingolimod (an S1P signaling molecule) is superior to IFN in preventing disability progression in newly diagnosed RRMS patients. Thus fingolimod served as the base for developing next-generation compounds with superior attributes, [7].

The new members of S1P receptor modulators such as (amiselimod, ozanimod, ponesimod, siponimod), have provided more control on MS as they might prevent synaptic neurodegeneration and promote remyelination in the central nervous system (CNS), [8].

The rationale of the current protocol

The management of the relapsing forms of MS (RRMS and SPMS with relapses) can be well achieved with versatile disease modifying treatments. Nevertheless, none of these modalities reliably provided efficacy in decelerating disability progression in the subgroup of subjects with SPMS. The current therapy for subjects with SPMS deserves further exploration for optimum control of disability. The efficacy and safety profile of a newly class known as S1P receptor modulators (amiselimod, ozanimod, ponesimod, siponimod) will assist to further optimize the management of MS and more specifically SPMS.

Objective

This protocol for systematic review will address the following questions:

1. Do S1P receptor modulators (amiselimod, ozanimod, ponesimod, siponimod) prove non-inferiority or superiority over placebo/comparator in subjects with any type/stage of MS?
2. Do S1P receptor modulators (amiselimod, ozanimod, ponesimod, siponimod) prove a safety profile comparable to other drug classes used in management of MS?
3. Is there any difference aligned between the members of the S1P class (amiselimod, ozanimod, ponesimod, siponimod)?

Aim of the review

The purpose of the protocol of the current systematic review and meta-analysis is to assess, compare, and explore the efficacy and safety of S1P class members (amiselimod, ozanimod, ponesimod, siponimod) versus other modalities in terms of clinical improvement in disability and prognosis at the end of treatment in the intent-to-treat (ITT) population.

Ethics approval

Ethics approval is not required for this type of systematic review and meta-analysis.

METHODS

The current systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) website, [https://www.crd.york.ac.uk/prospero/#myprospero] ID: CRD42020199697. We will conduct a systematic review and meta-analysis (participants, interventions, comparisons and outcomes (PICO) on phase II and phase III randomized clinical trials (RCT) for MS.

Eligibility criteria

We will conduct a systematic review and meta-analysis (PICO) on phase II and phase III RCT-s for subjects with MS who have received S1P.

Types of participants, interventions, comparisons and outcomes

Subjects diagnosed with any type of MS **(population)** and receiving any of the following S1P receptor modulators: amiselimod, ozanimod, ponesimod, siponimod (**intervention)** versus Placebo/comparator **(comparison)**. The primary efficacy endpoint will be the improvement in any of the following: SPMS, walk, disability and/or the composite of any of the aforementioned, time to 3-month complete disability progress (CDP) and percentage reduction in the monthly number of combined unique active lesions (CUALs) at 3 months. The secondary safety endpoint will be the development of adverse events during therapy with S1P (**outcomes**).

The **measure of effect** will be the reduction on disease markers and/or improvement of disability. The magnitude of difference between S1P and the placebo or the comparator will be of high priority and will be expressed as relative risks (RR), odds ratios (OR), risk difference, and/or number needed to treat.

The **inclusion criteria** will be the following: subjects diagnosed with MS (all types), adult ≥18 years, both genders, hospitalized and non-hospitalized, RCT design (phase II RCT or Phase III RCT), with placebo/comparator, subjects receiving intervention drug S1P (amiselimod, ozanimod, ponesimod, siponimod), trials published in English language, full-text articles, primary outcomes reported status of disability conducted on humans within the last years (2013 -2019). We will exclude the following: RCT with post-analysis studies, dose-finding RCT-s, non-RCT, retrospective trials, trial on pediatric population, trials which have evaluated other primary outcomes than the efficacy of S1P in MS. Furthermore, we will exclude trials that have been conducted on pregnant subjects and transplant subjects.

The **setting** will be out/in patients (hospitalized or not hospitalized). Trials will be retrieved during the period from the year 2013 to the year 2019, published in English language in full text.

The **search method** of trials retrieved will be conducted via Google Scholar and PubMed, for RCTs involving subjects with MS. The database was retrieved between the years 2013 to 2020 with the Medical Subject Headings (MeSH) search terms: multiple sclerosis (MS); "sphingosine-1-phosphate receptor modulator"; "Amiselimod"; "ozanimod"; "ponesimod"; "siponimod"; "randomized clinical trials", "placebo"; "comparator"; "safety"; "efficacy", which was shown as images in the supplementary material.

Types of studies

We have developed a protocol for the current systematic review and meta-analysis on the efficacy and safety profile of S1P (amiselimod, ozanimod, ponesimod, siponimod) with the primary endpoint of improvement in disability as measures by validated clinically approved tools. We will conduct the search for published RCT on English language reporting the efficacy and safety of S1P receptor modulators (amiselimod, ozanimod, ponesimod, siponimod). The current systematic review will be on RCT-s phase II and phase III subjects with MS (all types).

The **selection criteria** will be S1P alone compared to placebo or other modalities. The selected trials citations will be imported into systematic review managers/software (COVIDENCE https://www.covidence.org). In addition, we will use the manual searched citations with the same MeSH terms and conditions. All data will be collated by using the predefined Cochrane library approved structured modified forms. The draft of the search strategy to be used for one electronic database including planned limits is shown in, [**Figures 1 and 2**].

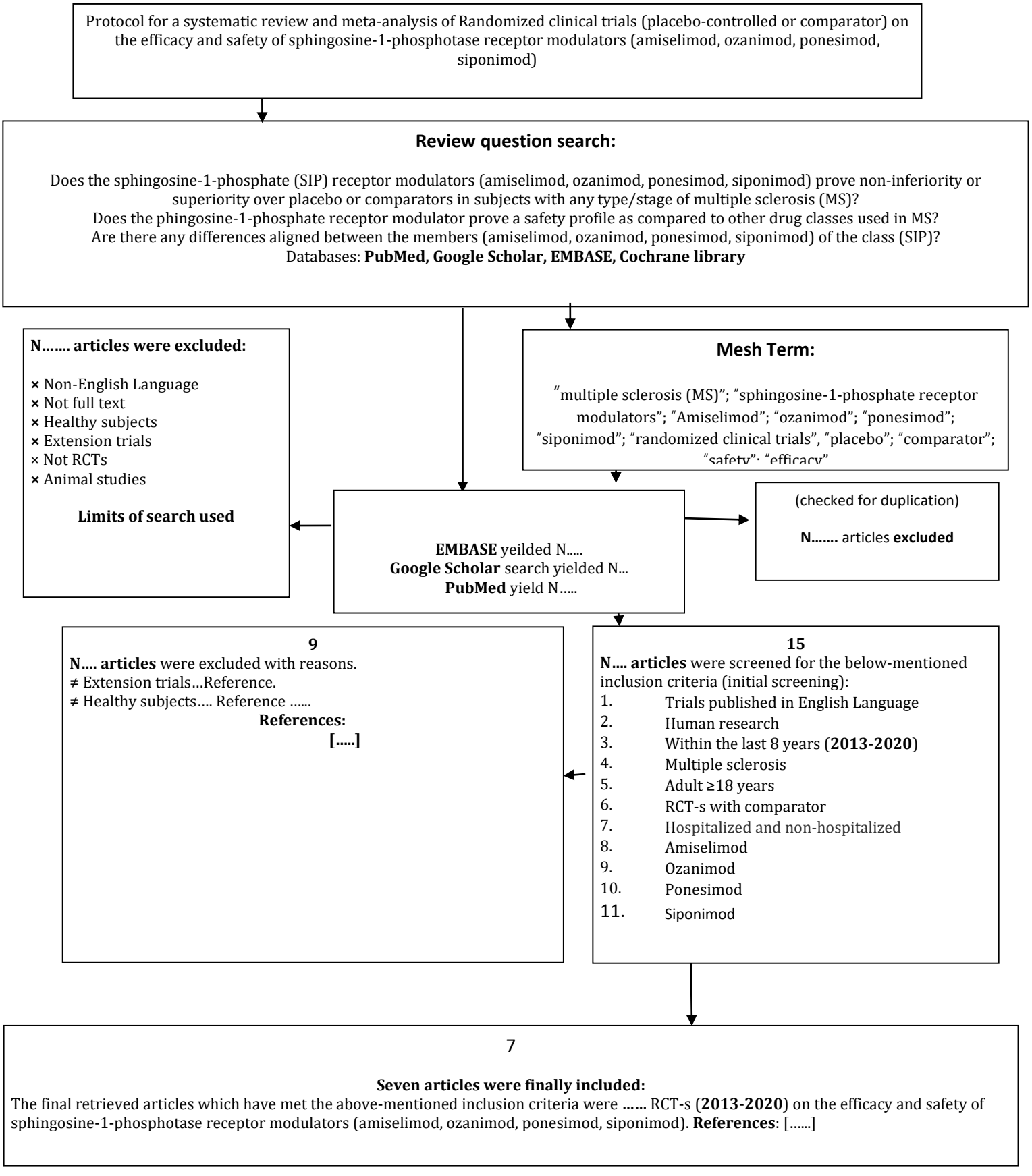
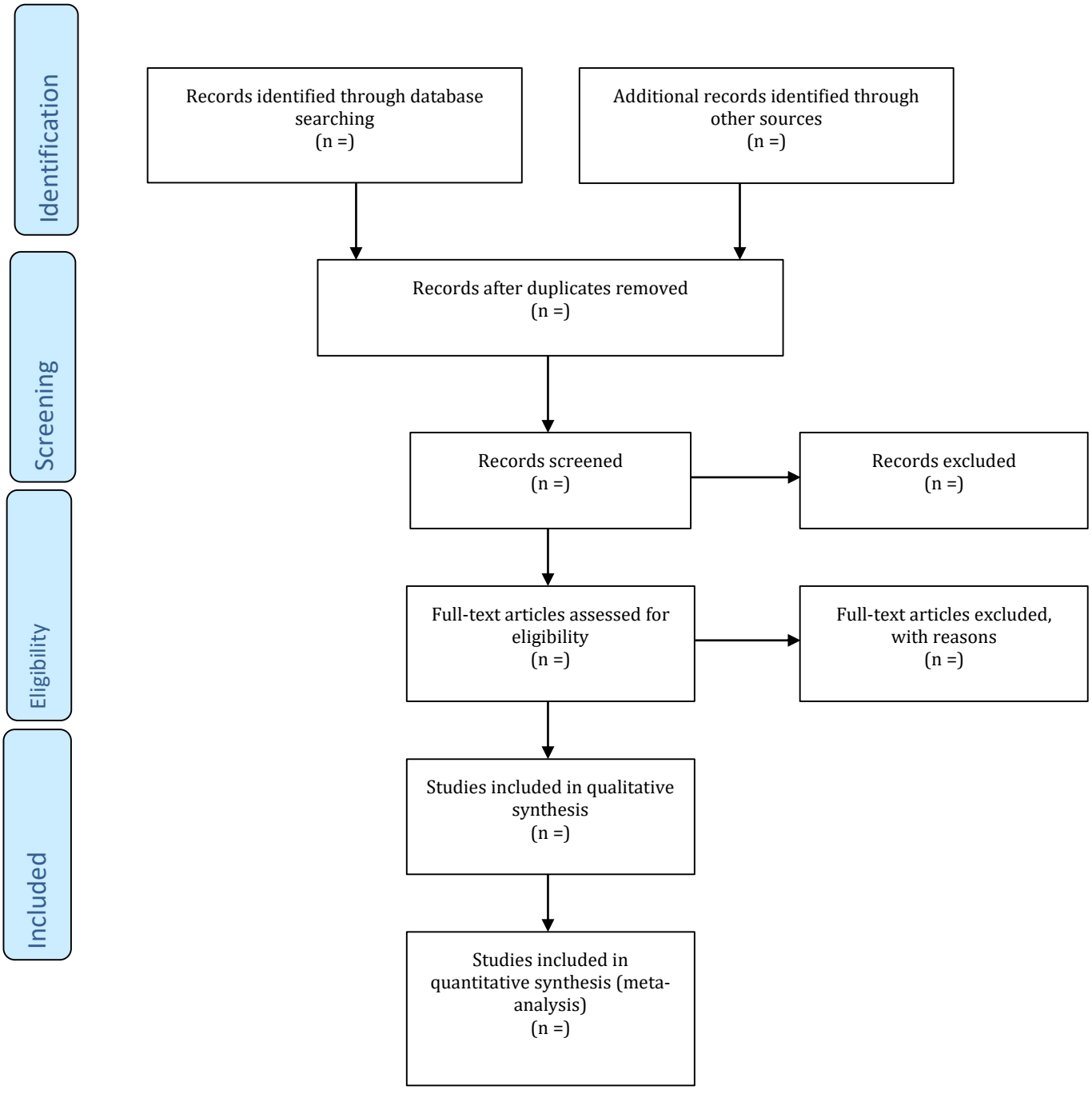


Figure 1: Flow diagram of included and excluded articles in the current systematic review and meta-analysis

PRISMA 2009 Flow Diagram



Data collection and analysis (data management) we will access full articles, screen and retrieve content with predefined checklist (Cochrane templates) developed and modified specifically to ensure the strict inclusion criteria. We will follow the checklist that has been adapted for use with protocol submissions to Systematic Reviews from Table 3 in Moher publication, [9].

Selection process the trials will be selected by all the authors based on the inclusion criteria. The methods will be used for identifying published trials in the official websites will be structured, predefined and specific MeSH terms for identifying eligible trials for inclusion in the current systematic review and meta-analysis. We will follow a strict checklist with pre-specified inclusion and exclusion criteria to ensure that the identified trials are as per the current systematic review methodology. The authors (AA, A Sadeq, NAK and HA) will double check the process and repeat the search terms individually and will compare between the attempts, whereby, discrepancies will be resolved with discussions in reporting.

The selected trials will be further reviewed by other different authors (IK, DN, EEGO, SMM, and JD) will be double checked by another different authors (JA, IMA, WSME, NA, and HSAA) and will be further verified by repeating the process mentioned above (HAA, MEH, SAAE, An Adel, ABA, AE and FHF). The final double checking and verification will ensure that the selected trials precisely met the final relevant information and primary outcome needed for the current systematic review and meta-analysis. The type of MS, trial duration, follow-up duration and primary end point (outcomes measures) will be shown in the supplementary material, [Appendix I]. The trials registration, DOI and author details, of the respective included RCT will be presented in, [Appendix II]. The safety outcomes (AEs) for the trials included in the current systematic review will be presented in, [Appendix III].

Data extraction and synthesis the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines will be used to abstract data and assess quality and validity. Data extraction (selection and coding) will be performed on the relevant variables from the original RCT and supplementary materials. The data extraction will contain trial registration, study country, number of involved countries (trial centers), type of MS, trial duration, follow-up duration, the efficacy data, primary endpoint (outcomes measures), the safety outcomes (adverse events) for the included trials. The above data will be collated with structured forms, verified, reviewed, double-checked, independently confirmed, and recorded in the final format in excel sheets and conveyed to the RevMan 5.4 databases.

Data items we will define all variables for which data will be sought (e.g., PICO items, funding sources), any pre planned data assumptions and simplifications. **PICO** items: We will conduct a systematic review and meta-analysis (PICO) on phase II and phase III RCT-s for subjects with MS who have received S1P. Subjects both gender with MS any type (**participants**) and receiving S1P (**intervention**) for primary prevention of disability events randomized versus placebo or comparator (**comparison**). The primary efficacy endpoint will be the clinical improvement in disability and prognosis at the end of treatment in the ITT population (**outcomes**).

Outcomes and prioritization (**Outcome measures)** the primary outcome measure will be the clinical improvement in disability and prognosis at the end of treatment in the ITT population (**outcomes**). The differences in treatment (effect size) between the intervention drug (S1P) and placebo/comparators as non-inferiority or superiority will be reported. The **measures of effect** will be the reduction on disease markers and/or improvement of disability. The magnitude of difference between S1P and the placebo or the comparator will be of high priority, [**Figure 3**].

Figure 3: Characteristics of randomized controlled trials with placebo and/or active comparator included articles (PICO)

Participants: Subjects with multiple sclerosis; population size: the number of randomized subjects in each arm of the trial; proportion of males versus females; age range (mean ± SD); BMI (mean ± SD); and relevant baseline clinical characteristics of recruited subjects.

Interventions Sphingosine-1-phosphate (S1P) receptor modulators (amiselimod; ozanimod; ponesimod; siponimod) (different doing) versus placebo or the comparator doses (**Comparators**) such as interferon beta-1a.

Outcomes:
A. The primary outcome measures: -

- ARR over 3/12/24 months based on confirmed, protocol-defined relapses.
- Time to 3-month CDP defined as a1-point increase in EDSS
- Number of gadolinium-enhanced T1-weighted lesions from weeks 8-24
- Cumulative number of total gadolinium-enhancing lesions on MRI at weeks 12–24
-

B. The Secondary outcome measures:

- Time to 3-month confirmed worsening of at least 20% from baseline in the T25FW
- ARR and time to first confirmed relapse within 24 weeks of ponesimod initiation
- Effect of siponimod on the number of monthly CUALs (T1,2 lesions)
- Number of gadolinium-enhancing lesions at week 24
- other secondary outcomes as arises

Key words: - amiselimod; comparator; efficacy; multiple sclerosis (MS); ozanimod; placebo; ponesimod; randomized clinical trials (RCTs), safety; siponimod; sphingosine-1-phosphate (S1P) receptor modulators

Risk of bias in individual studies

Quality of RCT-s and assessment of risk of bias in order to minimize and avoid bias in the selection of RCT-s (both at study level and outcome) for the current systematic review and meta-analysis, the quality of the RCT-s will be evaluated based on the five-point scale outlined by Jadad, [10].

We will assess the risk of bias in trials by confirming the following points: the randomization technique (with proper concealment of the allocation sequence), blinding

(subjects and investigator to treatment allocation) with a description of the blinding method for maintaining prognostic groups balance, completeness of follow up, reporting discontinuation, loss to follow-up, and failure to adhere to the ITT principle; performing analyses considering all subjects for whom outcome data are clinically evaluable; there is no selective outcome reporting and finally no use of any invalidated outcome measures. The risk of bias tool, version 2.0 (Cochrane) will be used for the risk of bias assessment.

Data synthesis 15a Describe criteria under which study data will be quantitatively synthesized the purpose of this systematic review is to assess the efficacy and safety of S1P, compare and explore the efficacy and safety of S1P versus other treatment modalities in terms of improvement in disability. The data synthesis will be quantitative, descriptive data will be presented, and inferential statistics and meta-analysis will be performed.

Exploration of variation in effects (quantitative synthesis)**:** The variations of effects (heterogeneity) in the RCTs included in the current systematic review and meta-analysis comprised a set of clinical covariates (clinical heterogeneity) from the relevant population level (matched groups of MS), the intervention level (intervention vs. comparator), outcomes level (ITT: clinical success, superiority/inferiority and statistical magnitude of difference) and planned summary measure.

Our meta-analysis will be executed by utilizing Revman 5.4 to collate data and explore consistencies amide trials. The Mantel-Haenszel (MH) method along with the random-effects model will be used for each primary outcome. The pooled estimates of odds ratio (OR) with 95% confidence interval (CI) will be estimated and demonstrated. To examine heterogeneity among individual study effect sizes we will use I2 index, tau squared, and the Q-test along with P-value (considered statistically significant at less than 0.05). To reduce bias risk, independent pooling of data from RCTs will be executed and funnel plots and Egger's linear regression test of funnel plot asymmetry will be prepared to assess publication bias. A sensitivity analysis will be conducted to investigate potential sources of inconsistency. We will generate forest plots to show the relative effect size of intervention and comparator for each clinical outcome. Meta-regression techniques will be utilized to inspect the potential sources of heterogeneity.

Proposed additional analyses we will conduct a meta-analysis in the current systematic review as well as reporting the sensitivity analysis. However, we also plan structured synthesis of data and comparison between the inferences in the respective trials (e.g., sensitivity and/or subgroup analyses and/or meta-regression). Data will be pooled using random-effects models.

Meta-bias: Publication bias is defined as the failure to publish the results of a study on the basis of the direction or strength of the study findings. In the current systematic review and meta-analysis we will use a funnel plot to check for the existence of publication bias or systematic heterogeneity in the studies taken for analysis. We will use Egger's regression for quantifying funnel plot asymmetry or Rosenthal's fail-safe number or "fail-safe N method". We have planned to avoid selective reporting within trials by not excluding non-significant study outcomes and by describing structured search criteria based on published methodologies.

Confidence in cumulative evidence we will assess the strength of evidence of the final results in a GRADE Evidence Profile (GEP). This GEP will contain the PICO question, the type and number of trials included the number of participants in the trials, the effect sizes and their confidence intervals and the grading of the quality of the evidence and its starting level and reasons for upgrading or downgrading the quality. The quality of evidence for all outcomes for included trials will be judged using an adaptation of the GRADE methodology assessment, [10-13]. The quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias.

Anticipated results

We will present the systematic review results and the meta-analysis results in complete tables based on PICO comparison between the included trials. The results will contain a systematic critical evaluation of the included RCT-s in terms of the number of the population (characteristics), the dosing of intervention (sphingosine-1-phosphate receptor modulators), dosing of the comparators and the main outcome measures. The necessary elements of PRISMA will be strictly followed to report the systematic review. The meta-analysis will be reported with the Cochrane guidelines in synthesis of RCT-s and all forms will be based on the quality measures as per the validated Cochrane templates.

TABLE 1 2010 McDonald MRI Criteria for Demonstration of dissemination of lesions (DIS)

DIS Can Be Demonstrated by 1 T2 Lesion[a] in at Least 2 of 4 Areas of the CNS:
○ Periventricular ○ Juxtacortical ○ Infratentorial ○ Spinal cord[b] Based on Swanton et al [21,22].
MRI ¼ magnetic resonance imaging; DIS ¼ lesion dissemination in space; CNS ¼ central nervous system
[a]Gadolinium enhancement of lesions is not required for DIS. [b]If a subject has a brainstem or spinal cord syndrome; the symptomatic lesions are excluded from the Criteria and do not contribute to lesion count.

T1 and T2

- T1 and T2 refer to the time taken between magnetic pulses and the image is taken.
- These different methods are used to detect different structures or chemicals in the CNS. T1 and T2 lesions refers to whether the lesions were detected using either the T1 or T2 method.
- A T1 MRI image supplies information about current disease activity by highlighting areas of active inflammation.
- A T2 MRI image provides information about disease burden or lesion load (the total amount of lesion area, both old and new).]

Keys:
CNS: central nervous system; **DIS**: dissemination of lesions; **MRI**: magnetic resonance imaging

DISCUSSION

The role of sphingosine-1-phosphate receptor modulators (amiselimod; ozanimod; ponesimod; siponimod) has emerged in the recent years with effective remissions, minimized relapses improved clinical outcomes and safety profile.

The current systematic review and meta-analysis will provide evidence by synthesis of well-designed and robust RCT-s conducted on (amiselimod; ozanimod; ponesimod; siponimod). We intend to minimize the publication bias and reporting bias with the use of published technical methods as mentioned-previously in the protocol. We intend to share our findings with the academia and MS societies worldwide.

In previously MS modalities, the no evidence of disease activity concept (a term used in retrospective analysis of the AFFIRM natalizumab) was defined in terms of the absence of relapses and disability progression, absence of new T2 lesion and increased T2 lesion volume (disease activity-3), brain volume loss (disease activity-4) and/or aggregate outcome of both clinical and MRI disease activity. Later cognitive measures was added in this composite (no evidence of disease activity-5), however, more recently a different definition of no evidence of disease activity-5 has been proposed to include serum neurofilament light.

The current systematic review and meta-analysis will provide highly relevant findings of evidence for the role of sphingosine-1-phosphate receptor modulators (amiselimod; ozanimod; ponesimod; siponimod) in the management of MS, [14-20].

In superiority RCT of 1138 participants were randomly assigned to daily oral ozanimod 1.0 mg or 0.5 mg or weekly IM interferon beta-1a 30 µg. Ozanimod was superior to interferon beta-1a and was associated with less discontinuation but similar incidence of infections, [14]. Another superiority RCT of 1255 participants, has shown that ozanimod was well tolerated, with a lower incidence of TEAEs than interferon beta1a, [15]. Siponimod was superior to placebo over three years RCT of 1651 participants with lower relapse rate, [16[, however earlier trials did not show such reduction, [17].

Amiselimod 0.2 and 0.4 mg for 24 weeks versus placebo in a RCT of 381 participants, compared with placebo, has shown lower median number of lesions, reduced both total number of gadolinium-enhanced T1-weighted lesions and total number of new or enlarged T2-weighted lesions. Furthermore, amiselimod has delayed time to first relapse versus placebo. Aniselimod was well tolerated except for headache and nasopharyngitis but no cardiac side-effects, [18]. Oral ponesimod 10, 20 and 40 mg oral versus placebo in 393 has shown lower number of new T1 Gd+ lesions and increased time to relapse, [19]. In earlier small RCT ponesimod 10 mg, 2 mg, 0.5 mg, or placebo in 106 participants reduced the number of CUALs (10 mg); with drug discontinuation with mitigated brady-arrhythmia in lower doses, [20].

CONCLUSION

This protocol will report the differences in the efficacy and safety of sphingosine-1-phosphate receptor modulators (intervention) as compared to the placebo or other modalities (comparators).

Impact of findings on clincial practice

- Sphingosine-1-phosphate receptor modulators might have better benefit-risk profile that provides option for management of multiple sclerosis.
- Sphingosine-1-phosphate receptor modulators might be clinically effective in short and long-term for multiple sclerosis relapses, magnetic resonance imaging lesions, and disability progression.
- Sphingosine-1-phosphate receptor modulators might provide better safety profile with improved patient's satisfaction with transient and rare serious adverse events.
- Sphingosine-1-phosphate receptor modulators may permit clinicians to make informed decisions about the most efficacious and safest regimen for their clients.
- Sphingosine-1-phosphate receptor modulators may permit clinicians to enforce evidence-based clinical practices and add to the gained knowledge of such therapy.

Conflicts of interest/Competing interests No conflicts of interest or competing interests

Authors' contributions

We declare that AAE, A Sadeq, AAE, FHF, NAK, HA, NMAZ, IYK, DN, ABA, AE, AAL, SMES, MEH, NA, EEGO, SMA, JD, JA, IMA, WSME, NTALI, HSAA, HAA, SAAE, A Adel, and WMAK, have made substantial contributions to the conception, design of the work; the acquisition, analysis, interpretation of data, drafted the work, revised it critically for important intellectual content, approved the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The below protocol is intended for publication (we will follow Cochrane library instructions in developing the protocol)

ACKNOWLEDGEMENT

We would like to thank Dr. Noor Alhuda Kassem, Dr. Haia Abdulsamad and Dr. Doaa Nassar for their dedicated work in leading the group.

REFERENCES

1. Santinelli FB, Sebastião E, de Oliveira M, Barbieri FA. Multiple sclerosis: Implications for future research on postural control and gait. Brazilian Journal of Motor Behavior. 2020;14(2):46-49. DOI: 10.20338/bjmb.v14i2.169.
2. Aslani N, Ahmadi M, Samadbeik M. A systematic review of the attributes of electronic personal health Records for Patients with multiple sclerosis. Health and Technology. 2020;10(3):587-599. DOI: 10.2196/jmir.5876.
3. Mohammed EM. Multiple sclerosis is prominent in the Gulf states. Pathogenesis. 2016;3(2):19-38. DOI: 10.1016/j.pathog.2016.04.001.
4. Inojosa H, Proschmann U, Akgün K, Ziemssen T. A focus on secondary progressive multiple sclerosis (SPMS): challenges in diagnosis and definition. Journal of neurology. 2019:1-2. DOI: 10.1007/s00415-019-09489-5.
5. TAŞKAPILIOĞLU Ö. Recent Advances in the Treatment for Multiple Sclerosis; Current New Drugs Specific for Multiple Sclerosis. Archives of Neuropsychiatry/Noropsikiatri Arsivi. 2018;55. DOI: 10.29399/npa.23402.
6. Goldschmidt CH, Hua LH. Re-Evaluating the Use of IFN-β and Relapsing Multiple Sclerosis: Safety, Efficacy and Place in Therapy. Degenerative Neurological and Neuromuscular Disease. 2020; 10:29. DOI: 10.2147/DNND.S224912.
7. von Wyl V, Benkert P, Moser A, Lorscheider J, Décard B, Hänni P, et al. Disability progression in relapse-free multiple sclerosis patients on fingolimod versus interferon-beta/glatiramer acetate. Multiple Sclerosis Journal. 2020. DOI: 10.1177/1352458520918489.
8. Cohan S, Lucassen E, Smoot K, Brink J, Chen C. Sphingosine-1-Phosphate: Its Pharmacological Regulation and the Treatment of Multiple Sclerosis: A Review Article. Biomedicines. 2020;8(7):227. DOI : 10.3390/biomedicines8070227.
13. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015 Jan 1;4(1):1. doi: 10.1186/2046-4053-4-1.
10. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12. DOI: 10.1016/0197-2456(95)00134-4.
11. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-406. DOI: 10.1016/j.jclinepi.2010.07.015.
12. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-394. DOI: 10.1016/j.jclinepi.2010.04.026.
13. Morgan RL, Thayer KA, Bero L, Bruce N, Falck-Ytter Y, Ghersi D, et al. GRADE: Assessing the quality of evidence in environmental and occupational health. Environ Int. 2016;92-93:611-616. DOI: 10.1016/j.envint.2016.01.004.
14. Cohen JA, Comi G, Selmaj KW, Bar-Or A, Arnold DL, Steinman L, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. The Lancet Neurology. 2019;18(11):1021-1033. DOI: 10.1016/S1474-4422(19)30238-8
15. Comi G, Kappos L, Selmaj KW, Bar-Or A, Arnold DL, Steinman L, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. The Lancet Neurology. 2019;18(11):1009-1020. DOI: 10.1016/S1474-4422(19)30239-X.
16. Kappos L, Bar-Or A, Cree BA, Fox RJ, Giovannoni G, Gold R, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. The Lancet. 2018; 391(10127):1263-1273. DOI 10.1016/S0140-6736(18)30475-6.
17. Cohen JA, Arnold DL, Comi G, Bar-Or A, Gujrathi S, Hartung JP, et al. RADIANCE Study Group. Safety and efficacy of the selective sphingosine 1-phosphate receptor modulator ozanimod in relapsing multiple sclerosis (RADIANCE): a randomised, placebo-controlled, phase 2 trial. The Lancet Neurology. 2016;15(4):373-381. DOI: 10.1016/s1474-4422(16)00018-1.
18. Kappos L, Arnold DL, Bar-Or A, Camm J, Derfuss T, Kieseier BC, et al. Safety and efficacy of amiselimod in relapsing multiple sclerosis (MOMENTUM): a randomised, double-blind, placebo-controlled phase 2 trial. The Lancet Neurology. 2016;15(11):1148-1159. DOI:
19. Olsson T, Boster A, Fernández Ó, Freedman MS, Pozzilli C, Bach D, et al. Oral ponesimod in relapsing–remitting multiple sclerosis: a randomised phase II trial. Journal of Neurology, Neurosurgery & Psychiatry. 2014;85(11):1198-1208. DOI: 10.1016/S1474-4422(16)30192-2.
20. Selmaj K, Li DK, Hartung HP, Hemmer B, Kappos L, Freedman MS, et al. Siponimod for patients with relapsing-remitting multiple sclerosis (BOLD): an adaptive, dose-ranging, randomised, phase 2 study. The Lancet Neurol. 2013;12(8):756-67. DOI: 10.1016/S1474-4422(13)70102-9.
21. Swanton JK, Rovira A, Tintore M, Altmann DR, Barkhof F, Filippi M, et al. MRI criteria for multiple sclerosis in patients presenting with clinically isolated syndromes: a multicentre retrospective study. The Lancet Neurology. 2007 Aug 1;6(8):677-686. DOI: 10.1016/S1474-4422(07)70176-X.
22. Swanton JK, Fernando K, Dalton CM, Miszkiel KA, Thompson AJ, Plant GT, et al. Modification of MRI criteria for multiple sclerosis in patients with clinically isolated syndromes. Journal of Neurology, Neurosurgery & Psychiatry. 2006 Jul 1;77(7):830-833. DOI: 10.1136/jnnp.2005.073247.

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	-
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	9
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1-4
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	5
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	4
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	4
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	4
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	8
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	9
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	9-10
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	10-11
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	11
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of	☒	☐	11

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		the review (i.e., screening, eligibility, and inclusion in meta-analysis)			
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	12
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	13
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	13
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	14
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	14
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	16
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	16