

Use of pragmatic randomized trials in Multiple Sclerosis: a systematic overview

Appendix 1. Search strategy

Initial search strategy in MEDLINE/Ovid; last search: December 1, 2022; hits: 257.

Note: For the pragmatic component of the search strategy (#1-#11), we selected a sensitivity-maximizing search for pragmatic trials that was designed for Ovid MEDLINE¹⁶. For the Multiple Sclerosis component, we selected keywords and controlled vocabulary that was used by the Canadian Agency for Drugs and Technologies in Health (CADTH)¹⁷.

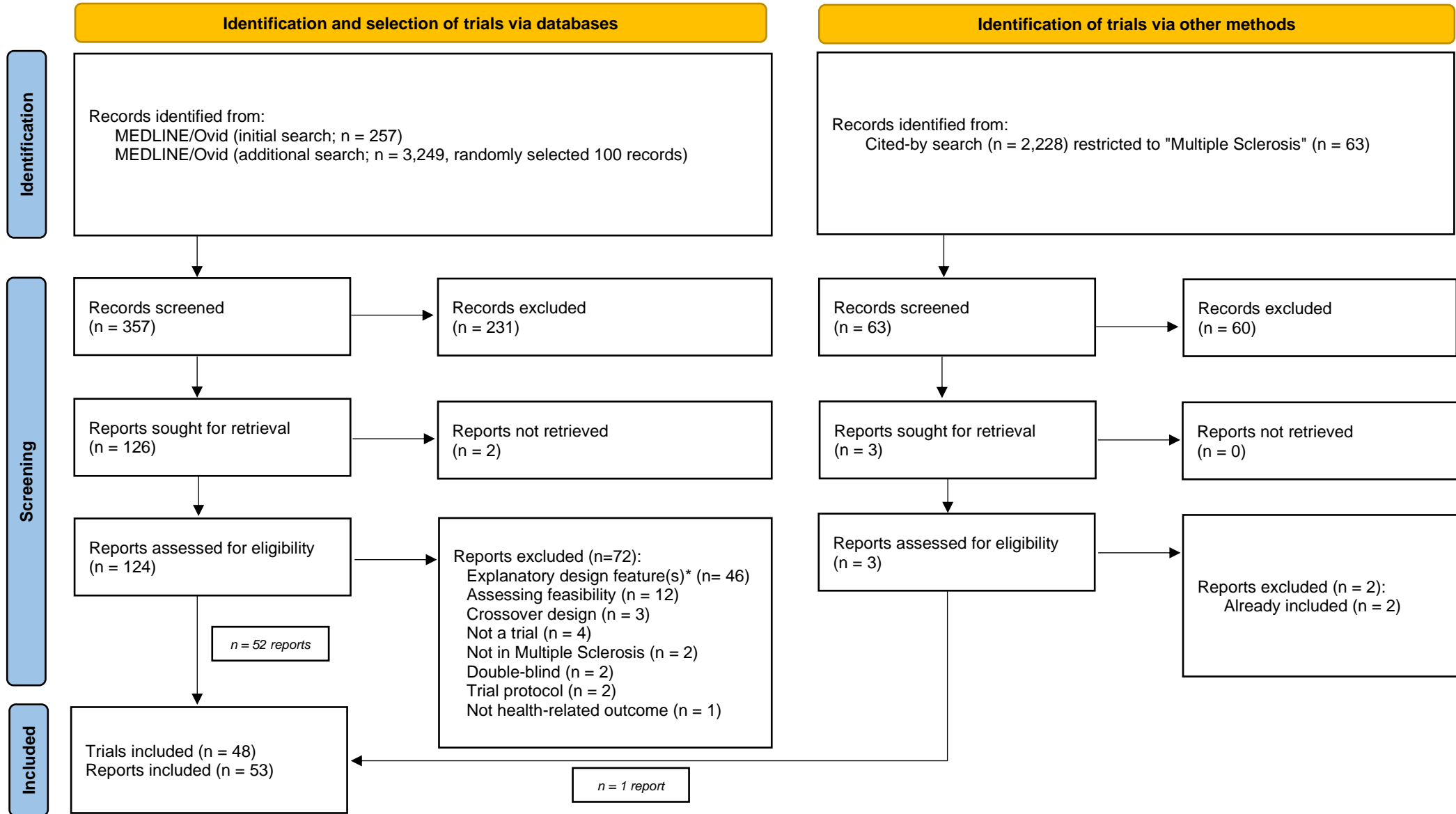
Search	Query
#1	((pragmatic\$ OR naturalistic OR real world OR real life OR unblinded OR unmasked OR cluster OR step\$ wedge\$ OR point of care OR factorial OR switchback OR switch back OR phase 4 OR phase IV) adj10 (study OR trial)) OR (practical trial OR effectiveness trial OR ((cluster\$ or communit\$) adj2 randomi\$)).tw.
#2	(general practice\$ OR primary care OR registry based OR health record\$ OR medical record\$ OR EHR OR EMR OR administrative data OR routinely collected data OR (communit\$ adj2 intervention\$) OR quality improvement OR implementation OR decision support OR health service\$ OR health system\$ OR comparative effectiveness OR CER OR usual care OR evidence based OR practice guideline\$ OR (guideline\$ adj1 recommend\$) OR knowledge translation OR health technology assessment OR HTA OR cost effectiveness OR process evaluation OR economic evaluation OR patient oriented).tw.
#3	randomized controlled trial.pt. OR ((comparative effectiveness OR randomi?ed) adj10 (trial OR study)).ti.
#4	(comment on OR phase 1 OR phase I OR phase 2 OR phase II OR non-randomi?ed OR quasi-randomi?ed OR pseudo-randomi?ed).ti. OR (clinical trial, phase I OR clinical trial, phase II OR systematic review OR meta-analysis OR review OR editorial).pt.
#5	pragmatic clinical trial.pt.
#6	1 or 2
#7	3 not 4
#8	6 and 7
#9	5 or 8
#10	exp Animals/ NOT Humans/
#11	9 NOT 10
#12	Multiple Sclerosis, Relapsing-Remitting/ or multiple sclerosis/
#13	(relapsing remitting adj2 multiple sclerosis).ti,ab,sh,hw,ot.
#14	(remitting relapsing adj2 multiple sclerosis).ti,ab,sh,hw,ot.
#15	((relapsing remitting adj2 ms) or (remitting relapsing adj2 ms)).ti,ab,sh,hw,ot.
#16	((exacerbate* or disseminated or insular or secondary progressive or primary progressive or progressive relapsing) adj2 (sclerosis or ms)).ti,ab,sh,hw,ot.
#17	(rrms or encephalomyelitis disseminat*).ti,ab,sh,hw,ot.
#18	12 or 13 or 14 or 15 or 16 or 17
#19	sclerosis.ab,ti.
#20	18 or 19
#21	11 AND 20

To quantify the sensitivity of the above search strategy for pragmatic trials, we selected a random sample of 100 articles identified in MEDLINE/Ovid (last search 19 December 2022; hits: 3249) with a randomized trials filter combined with the MS search strategy but without applying restrictions for pragmatic trials.

Note: For the trial component of the search strategy (#1-#11), we adapted the focused search strategy (Appendix 1) and selected the keywords and controlled vocabulary related to trials¹⁶. For the Multiple Sclerosis component, we selected keywords and controlled vocabulary that was used by the Canadian Agency for Drugs and Technologies in Health (CADTH)¹⁷.

Search	Query
#1	randomized controlled trial.pt. OR ((comparative effectiveness OR randomi?ed) adj10 (trial OR study)).ti.
#2	(comment on OR phase 1 OR phase I OR phase 2 OR phase II OR non-randomi?ed OR quasi-randomi?ed OR pseudo-randomi?ed).ti. OR (clinical trial, phase I OR clinical trial, phase II OR systematic review OR meta-analysis OR review OR editorial).pt.
#3	1 not 2
#4	pragmatic clinical trial.pt.
#5	3 or 4
#6	exp Animals/NOT Humans/
#7	5 not 6
#8	Multiple Sclerosis, Relapsing-Remitting/ or multiple sclerosis/
#9	(relapsing remitting adj2 multiple sclerosis).ti,ab,sh,hw,ot.
#10	(remitting relapsing adj2 multiple sclerosis).ti,ab,sh,hw,ot.
#11	((relapsing remitting adj2 ms) or (remitting relapsing adj2 ms)).ti,ab,sh,hw,ot.
#12	((exacerbate* or disseminated or insular or secondary progressive or primary progressive or progressive relapsing) adj2 (sclerosis or ms)).ti,ab,sh,hw,ot.
#13	(rrms or encephalomyelitis disseminat*).ti,ab,sh,hw,ot.
#14	8 or 9 or 10 or 11 or 12 or 13
#15	sclerosis.ab,ti.
#16	14 or 15
#17	7 AND 16

Appendix 2. Illustration of the literature search and study selection process



* At least one PRECIS-2 domain was assessed with 1 and/or 2 indicating more explanatory than pragmatic design features.

Appendix 3. Additional trial characteristics (n=48)

	n (%)
Publication year	
Until 2000	2 (4)
2001-2005	3 (6)
2006-2010	5 (10)
2011-2015	14 (29)
2016-2020	19 (40)
2021 and later	5 (10)
Journal	
Multiple Sclerosis Journal	11 (23)
Clinical Rehabilitation	8 (17)
Health Technology Assessment	3 (6)
Journal of Neurology, Neurosurgery, and Psychiatry	3 (6)
Multiple Sclerosis and Related Disorders	2 (4)
Neurology	2 (4)
Other (each one publication)	19 (40)
Country of conduct *	44 (92)
UK	18 (38)
Italy	6 (13)
Denmark	5 (10)
US	5 (10)
Australia	4 (8)
Belgium	4 (8)
Canada	4 (8)
France	4 (8)
Spain	4 (8)
Other	9 (19)
Number of randomized patients	
< 100	28 (58)
101-200	12 (25)
201-300	1 (2)
301-400	2 (4)
401-500	2 (4)
> 500	3 (6)
Unit of randomization	
Participant	47 (98)
Cluster	1 (2)
Number of trial arms	
2	45 (94)
3	2 (4)
4	1 (2)
Blinding (of outcome assessors)	
Yes	10 (21)
Partly	3 (6)
No	28 (58)
Unclear	7 (15)

Abbreviations: n = Number; UK = United Kingdom; US = United States.

Appendix 4. PRECIS-2 assessment of individual trials (n=48)

	Self-labelled as "pragmatic"	Eligibility criteria	Eligibility criteria (cluster-randomized trials)	Recruitment	Recruitment (cluster-randomized trials)	Setting	Organization	Flexibility – intervention delivery	Flexibility – intervention adherence	Follow-up	Primary outcome	Primary analysis
Arntzen et al. [22,80]	No	3	-	4	-	5	4	5	4	4	5	5
Boesen et al. ²³ *	Yes	4	-	5	-	4	5	5	NI	4	5	5
Bogosian et al. ²⁴	No	5	-	4	-	5	4	3	NI	3	5	5
Calkwood et al. ⁶⁴	No	3	-	5	-	5	5	NI	NI	4	5	5
Callesen et al. ²⁵	No	4	NI	4	NI	5	5	5	5	4	5	3
Carter et al. ²⁷	No	3	-	4	-	4	5	5	3	4	5	4
Cooper et al. ²⁶	No	4	-	4	-	5	5	5	4	4	5	4
Cutter et al. ²⁸	No	4	-	NI	-	5	NI	NI	4	3	5	5
Dodd et al. ²⁹	No	4	-	3	-	5	5	NI	4	4	5	4
Feys et al. ³⁰ *	Yes	3	-	4	-	5	2	5	2	1	3	3
Finch et al. ³¹ *	Yes	5	-	5	-	4	5	5	NI	NI	5	NI
Freeman et al. ²⁶ *	Yes	5	-	5	-	5	4	3	2	3	5	3
Garrett et al. ³³ *	Yes	5	-	5	-	5	NI	3	3	5	5	2
Giovannoni et al. ³⁴	No	3	-	NI	-	5	NI	NI	NI	4	5	NI
Grossman et al. ³⁵	No	5	-	4	-	3	5	NI	5	5	5	5
Gunn et al. ^{36,79} *	Yes	4	-	4	-	5	5	5	4	4	5	4
Hermens et al. ^{37,81}	No	4	-	NI	-	4	5	NI	NI	4	5	NI
Higginson et al. ³⁸	No	4	-	5	-	4	4	5	NI	4	5	4
Hoogstraten et al. ⁶⁵	No	5	-	NI	-	5	5	NI	NI	4	NI	NI
Humphreys et al. ³⁹	No	3	-	3	-	4	4	4	NI	4	5	5
Jongen et al. ⁴⁰	No	4	-	5	-	5	4	5	NI	4	5	3
Khayeri et al. ⁴¹	No	5	-	5	-	4	NI	4	NI	5	NI	NI
Kiropoulos et al. ⁴²	No	4	-	3	-	4	4	5	5	3	5	5
Langeskov-Christensen et al. ⁶⁶	No	5	-	NI	-	4	5	4	3	3	NI	5
Learmonth et al. ⁴³	No	4	-	5	-	5	5	3	3	4	5	3
Lincoln et al. ^{44,77} *	Yes	5	-	4	-	4	2	3	4	3	5	4
Mayo et al. ⁴⁵ *	Yes	4	-	4	-	5	5	5	2	3	1	2
Mazdeh et al. ⁶⁷	No	3	-	5	-	4	5	NI	NI	5	NI	NI
McClurg et al. ⁴⁶ *	Yes	5	-	4	-	5	3	5	3	2	5	4
Medina-Perez et al. ⁶⁸	No	4	-	5	-	4	4	3	3	3	NI	5
Millar et al. ⁶⁹	No	5	-	NI	-	5	5	5	NI	4	NI	NI
Miller et al. ⁴⁷	No	4	-	4	-	4	5	5	NI	4	5	NI
O'Hara et al. ⁴⁸	No	5	-	NI	-	4	3	5	NI	5	5	5
Papeix et al. ⁴⁹	No	4	-	5	-	4	5	5	NI	4	5	5
Paul et al. ⁵⁰ *	Yes	2	-	5	-	4	5	4	4	3	5	3
Pozzilli et al. ⁵¹	No	5	-	NI	-	5	3	5	NI	4	5	5
Renfrew et al. ⁵²	No	3	-	5	-	5	5	4	NI	4	5	NI
Riemenschneider et al. ⁶²	No	4	-	4	-	4	4	5	3	3	3	5
Solari et al. ⁵³	No	4	-	NI	-	5	5	5	NI	3	5	5
Straudi et al. ⁶³	No	5	-	5	-	4	4	5	3	4	5	5
Stuifbergen et al. ⁵⁴ *	Yes	5	-	3	-	5	3	NI	3	3	5	5
Thomas et al. ^{55,80} *	Yes	4	-	4	-	4	4	3	5	4	5	5
Torkhani et al. ⁵⁶	No	5	-	5	-	5	5	5	4	5	5	5
Velikonja et al. ⁵⁷	No	5	-	NI	-	4	4	NI	3	4	5	NI
Vermöhlen et al. ⁵⁸	No	3	-	NI	-	5	3	4	NI	4	5	5
Ward et al. ⁵⁹	No	5	-	4	-	4	4	5	NI	4	5	5
Weinstock-Guttman et al. ⁶⁰	No	5	-	NI	-	4	3	5	NI	3	4	NI
Williams et al. ⁶¹	No	4	-	NI	-	4	4	4	4	4	5	4

Abbreviations: - = Not applicable; NI = No sufficient information to assess the domain.

Notes: 1 = very explanatory; 2 = rather explanatory; 3 = equally pragmatic/explanatory; 4 = rather pragmatic; 5 = very pragmatic ⁷⁴; Notes: * Trials self-labelled as "pragmatic". References are provided in the main text of the publication.