

Comparative effectiveness of device-aided therapies on quality of life and off-time in advanced Parkinson's disease: a systematic review and Bayesian network meta-analysis

Angelo Antonini¹ ( <https://orcid.org/0000-0003-1040-2807>), Rajesh Pahwa² ( <https://orcid.org/0000-0003-3176-6466>), Per Odin³ ( <https://orcid.org/0000-0002-0756-7478>), Stuart H. Isaacson⁴ ( <https://orcid.org/0000-0002-9914-5706>), Aristide Merola⁵ ( <https://orcid.org/0000-0002-5587-726X>), Lin Wang,^{6,7} Prasanna L. Kandukuri,⁶ Ali Alobaidi^{6,8} ( <https://orcid.org/0000-0002-0720-7894>), Connie H. Yan ( <https://orcid.org/0000-0003-1467-4666>),^{6,8} Yanjun Bao,⁶ Cindy Zadikoff,⁶ Juan Carlos Parra⁶ ( <https://orcid.org/0000-0002-5613-6121>), Lars Bergmann,⁶ K. Ray Chaudhuri⁹ ( <https://orcid.org/0000-0003-2815-0505>)

¹*Parkinson and Movement Disorders Unit, Department of Neuroscience, University of Padova, Padova, Italy*

²*University of Kansas Medical Center, Kansas City, KS, USA*

³*University of Lund, Lund, Sweden*

⁴*Parkinson's Disease and Movement Disorders Center, Boca Raton, FL, USA*

⁵*The Ohio State University Wexner Medical Center, Department of Neurology, Columbus, OH, USA*

⁶*AbbVie Inc., North Chicago, IL, USA*

⁷*Johns Hopkins School of Public Health, Baltimore, MD, USA*

⁸*University of Illinois at Chicago, Chicago, IL, USA*

⁹*King's College and Parkinson Foundation Centre of Excellence, Kings College Hospital London, London, UK*

Corresponding author:

Angelo Antonini ( <https://orcid.org/0000-0003-1040-2807>)

Parkinson and Movement Disorders Unit

Department of Neuroscience

University of Padova

35128 Padova

Italy

Email: Angelo.antonini@unipd.it

Supplementary Table 1 Search strategy for the Medline and Embase databases

<i>Search Term</i>
1 Parkinson\$ disease.mp.
2 exp Parkinson Disease/
3 1 or 2
4 Deep brain stimulation/
5 (deep brain stimulation or dbs or subthalamic stimulation or pallidal stimulation or ventral intermediate nucleus stimulation or thalamic stimulation).ti,ab.
6 (4 or 5) and 3
7 limit 6 to English language
8 limit 7 to yr="2003 -Current"
9 exp "cost"/ or exp "cost benefit analysis"/
10 (animals not humans).sh.
11 (Clinical Conference or Consensus Development Conference or In Vitro or Meta-Analysis or Scientific Integrity Review or Twin Study or "Clinical Trial, Phase I" or Letter or News or Patient Education Handout or Review or Introductory Journal Article or Guideline or Practice Guideline or book or conference paper or editorial or letter or review or "journal: conference abstract" or short survey).pt.
12 (book or book series or conference paper or conference proceeding or "conference review" or editorial or letter or note or "review" or trade journal or addresses or autobiography or bibliography or biography or clinical conference or clinical trial, phase i or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or guideline or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or meta analysis or news or newspaper article or patient education handout or periodical index or practice guideline or "scientific integrity review" or systematic reviews or twin study or video-audio media or webcasts).pt,sh.
13 8 not (9 or 10 or 11 or 12)
14 case reports.pt.
15 case report/
16 13 not (14 or 15)
17 Apomorphine/ or apomorphine.ti,ab,nm.
18 Infusion Pumps/
19 (infusion\$ or pump\$ or infuse).ti,ab.
20 17 and (18 or 19)
21 20 and 3
22 limit 21 to English language
23 limit 22 to yr="2003 -Current"
24 (book or book series or conference paper or conference proceeding or "conference review" or editorial or letter or note or "review" or trade journal or addresses or autobiography or bibliography or biography or clinical conference or clinical trial, phase i or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or guideline or in vitro or interactive tutorial or

interview or introductory journal article or lectures or legal cases or legislation or meta analysis or news or newspaper article or patient education handout or periodical index or practice guideline or "scientific integrity review" or systematic reviews or twin study or video-audio media or webcasts).pt,sh.
25 23 not (24 or 9 or 10 or 11)
26 case reports.pt.
27 25 not (26 or 15)
28 duodopa.ti,ab,nm. or ((levodopa.ti,ab,nm. or levodopa/) and (carbidopa.ti,ab,nm. or carbidopa/)) or Duodopa/ or "carbidopa plus levodopa"/ or duodenal levodopa.ti,ab.
29 (intestin\$ or jejun\$ or duoden\$ or intrainestin\$ or intrajejun\$ or intraduoden\$).ti,ab.
30 28 and 29
31 30 and 3
32 limit 31 to English language
33 limit 32 to yr="2003 -Current"
34 (book or book series or conference paper or conference proceeding or "conference review" or editorial or letter or note or "review" or trade journal or addresses or autobiography or bibliography or biography or clinical conference or clinical trial, phase i or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or guideline or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or meta analysis or news or newspaper article or patient education handout or periodical index or practice guideline or "scientific integrity review" or systematic reviews or twin study or video-audio media or webcasts).pt,sh.
35 33 not (34 or 9 or 10 or 11)
36 case reports.pt.
37 35 not (36 or 15)
38 16 or 27 or 37
39 remove duplicates from 38
40 3 and (4 or 5 or 20 or 30)
41 limit 40 to (meta analysis or systematic reviews) [Limit not valid in Embase; records were retained]
42 ((literature adj3 review\$) or (systematic\$ adj2 (review\$ or overview))).ti,ab. or exp "Systematic Review"/
43 (meta?anal\$ or meta anal\$ or meta-anal\$ or metaanal\$ or metanal\$).ti,ab. or exp meta analysis/ or meta-analysis.pt,sh.
44 40 and (42 or 43)
45 41 or 44
46 limit 45 to English language
47 remove duplicates from 46
48 limit 47 to yr="2008 -Current"
49 39 or 48

Search strategy for the Cochrane Library

Search #	Search Term
#1	MeSH descriptor: [Parkinson Disease] explode all trees
#2	Parkinson* disease
#3	#1 or #2
#4	MeSH descriptor: [Deep Brain Stimulation] explode all trees
#5	deep brain stimulation or dbs or subthalamic stimulation or pallidal stimulation or ventral intermediate nucleus stimulation or thalamic stimulation
#6	(#4 or #5) and #3 from 2003, in Trials
#7	MeSH descriptor: [Apomorphine] explode all trees
#8	apomorphine
#9	MeSH descriptor: [Infusion Pumps] explode all trees
#10	infusion* or pump* or infuse
#11	(#7 or #8) and (#9 or #10)
#12	#11 and #3 from 2003, in Trials
#13	duodopa or (levodopa and carbidopa)
#14	MeSH descriptor: [Levodopa] explode all trees
#15	MeSH descriptor: [Carbidopa] explode all trees
#16	#14 and #15
#17	intestin* or jejun* or duoden*
#18	(#13 or #16) and #17
#19	#18 and #3 from 2003, in Trials
#20	#6 or #12 or #19 from 2003, in Trials
#21	(#4 or #5) and #3
#22	#11 and #3
#23	#18 and #3
#24	#21 or #22 or #23 from 2008, in Cochrane Reviews (Reviews and Protocols) and Other Reviews
#25	#20 or #24

Search strategy for the PubMed database

Search #	Search Term
#1	Search (Parkinson*[Title/Abstract] OR "paralysis agitans"[Title/Abstract])
#2	Search "parkinson disease"[MeSH Terms]

#3	Search (("brain excitation"[Title/Abstract] OR "brain stimulation"[Title/Abstract] OR "brain stimulus"[Title/Abstract] OR "deep brain stimulation"[Title/Abstract] OR "electrical brain stimulation"[Title/Abstract] OR "excitation,brain"[Title/Abstract] OR "brain depth stimulation"[Title/Abstract] OR "Brain Stimulation, Deep"[Title/Abstract] OR ("Electrical Stimulation"[Title/Abstract] AND Brain)[Title/Abstract] OR DBS[Title/Abstract]))
#4	Search "deep brain stimulation"[MeSH Terms]
#5	Search ((Duodopa[Title/Abstract] OR duopa[Title/Abstract] OR lcig[Title/Abstract]))
#6	Search ((levodopa[Title/Abstract] OR "l dopa"[Title/Abstract] OR "levo dopa"[Title/Abstract] OR levocarb[Title/Abstract] OR levodopacarbido[Title/Abstract] OR lcig[Title/Abstract] OR "carbidopa plus levodopa"[Title/Abstract] OR "levodopa plus carbidopa"[Title/Abstract] OR "carbidopa levodopa"[Title/Abstract] OR "L dopa carbidopa"[Title/Abstract] OR "levodopa carbidopa"[Title/Abstract] OR "levo dopa carbidopa"[Title/Abstract] OR DUODOPA[Title/Abstract] OR duopa[Title/Abstract]))
#7	Search (((intestin*[Title/Abstract] AND (gel[Title/Abstract] OR gels[Title/Abstract] OR infus*))[Title/Abstract] OR "enteral suspension"[Title/Abstract] OR "enteral suspensions"[Title/Abstract] OR "intestinal gel"[Title/Abstract] OR "intestinal gels"[Title/Abstract] OR intestin*[Title/Abstract]))
#8	Search (("CSAI"[Title/Abstract] OR (apomorphine AND (subcutaneous* OR infusion* OR continuous)))[Title/Abstract]))
#9	Search ((apomorphine[Title/Abstract] AND subcutaneous*[Title/Abstract]))
#10	Search ((apomorphine[Title/Abstract] AND infusion*[Title/Abstract]))
#11	Search ((apomorphine[Title/Abstract] AND continuous[Title/Abstract]))
#12	Search (#1 or #2)
#13	Search (#3 or #4 or #5 or (#6 and #7) or #9 or #10 OR #11)
#14	Search ((efficacy[Title/Abstract] OR efficacious*[Title/Abstract] OR effective*[Title/Abstract] OR "therapeutic effect"[Title/Abstract] OR "desired effect"[Title/Abstract] OR "therapeutic effects"[Title/Abstract] OR "desired effects"[Title/Abstract]))
#15	Search "activities of daily living"[MeSH Terms]
#16	Search ((ADL[Title/Abstract] OR ((activity[Title/Abstract] OR activities)[Title/Abstract] AND daily)[Title/Abstract] AND ((life[Title/Abstract] OR living)[Title/Abstract])) OR (chronic[Title/Abstract] AND limit*[Title/Abstract] AND (activity[Title/Abstract] OR activities[Title/Abstract]))
#17	Search (((longterm[Title/Abstract] OR "long term"[Title/Abstract] OR long-term[Title/Abstract])) OR (outcome[Title/Abstract] OR outcomes[Title/Abstract] OR out-come[Title/Abstract] OR out-comes[Title/Abstract] OR "out come"[Title/Abstract] OR "out comes"[Title/Abstract])) OR (unmet[Title/Abstract] OR "not met"[Title/Abstract] OR "not meet"[Title/Abstract] OR (meet*[Title/Abstract] AND (need[Title/Abstract] OR needs))[Title/Abstract]))
#18	Search "parkinson disease"[MeSH Major Topic]
#19	Search (#14 or #15 or #16)
#20	Search (#12 and #13 and #19)
#21	Search (#20 and #18)
#22	Search (#21 and #17)

#23	Search (#21 and #17) Filters: Humans
#24	Search (#21 and #17) Filters: Humans; English
#25	Search (#21 and #17) Filters: Publication date from 2016/12/31 to 2019/06/13; Humans; English

Search strategy for the BIOSIS Previews, Derwent Drug File, Embase, International Pharmaceutical Abstracts, Medline, and SciSearch databases

Search #	Search Term
#1	Parkinson* OR "paralysis agitans" OR "Parkinson's"
#2	MESH.EXACT("Parkinson Disease") OR EMB.EXACT("Parkinson disease") OR su("parkinson disease" OR "parkinson's disease")
#3	"brain excitation" OR "brain stimulation" OR "brain stimulus" OR "deep brain stimulation" OR "electrical brain stimulation" OR "excitation,brain" OR "brain depth stimulation" OR "Brain Stimulation, Deep" OR ("Electrical Stimulation" N/3 Brain) OR DBS
#4	EMB.EXACT("brain depth stimulation") OR MESH.EXACT("Deep Brain Stimulation") OR SU("brain depth stimulation" or "deep brain stimulation")
#5	Duodopa or duopa or lcig
#6	("atamet" OR "nacom" OR "sinemet") N/3 ((intestinal near/2 gel*) or gel* or " enteral suspension*" or "intestinal gel**")
#7	(levodopa or "l dopa" or "levo dopa" or levocarb or levodopacarbidoa or lcig or "carbidopa plus levodopa" or "levodopa plus carbidopa" OR "carbidopa levodopa" OR "L dopa carbidopa" OR "levodopa carbidopa" or "levo dopa carbidopa" OR DUODOPA or duopa) N/3 (([*]intestin[*] N/2 (gel* or gel or gels or infus[*4])) OR " enteral suspension*" or "intestinal gel**" OR *intestin*)
#8	EMB.EXACT("carbidopa plus levodopa") OR SU,subst("carbidopa plus levodopa" or "levodopa plus carbidopa")
#9	"CSAI" or (continuous N/3 ("sub q" OR subcutaneous[*2] OR "sub cutaneous[*2]" or SC OR sq OR "sub cu" OR subq OR subcut*) N/3 apomorphine N/3 infusion[*1])
#10	ab,tio,if(s1) and s2
#11	(ab,tio,if(s3) and s4) or (ab,tio,if,subst(s5 or s6 or s7) and s8) and ab,tio,if,subst,su(s9)
#12	(efficacy or efficacious[*4] or effective[*4] or "therapeutic effect[*1]" or "desired effect[*1]")
#13	EMB.EXACT.EXPLODE("drug efficacy") OR MESH.EXACT.EXPLODE("Treatment Outcome") OR (su("Treatment Outcome") OR su((drug OR therapy OR treatment) p/1 efficacy))
#14	ADL or (activit[*3] N/3 daily N/3 (living or life)) or (chronic N/3 limit[*6] N/3 activit[*3])
#15	EMB.EXACT("daily life activity") OR MESH.EXACT.EXPLODE("Activities of Daily Living") OR MESH.EXACT("Activities of Daily Living") OR SU("daily life activit[*3]" or "activit[*3] of daily living")
#16	(ab,tio,if(s12) and s13) or (ab,tio,if(s14) or s15)
#17	s10 and s11 and s16
#18	(pd(20170101-20190607) or ud(20170101-20190607)) and (py(2017-2019) or yr(2017-2019))
#19	s17 and s18

#20	ab,tio(("long term" or "long-term" or longterm) N/5 s12)
#21	ab,tio((outcome[*1] or "out come[*1]" or "out-come[*1]") N/5 s14)
#22	s19 and (s20 or s21)
#23	s19 and ab,tio((unmet or "not met" or ("not" N/3 meet[*3])) N/3 need[*1])
#24	s19 and tio(s1) and tio(s3 or s5 or s6 or s7 or s9)
#25	s19 and tio(s3 or s5 or s6 or s7 or s9) and tio(s12 or s14)
#26	s22 or s23 or s24 or s25
#27	s26 and la(English)
#28	s27 and (human(yes) or su(human or humans) or mesh(humans) or emb(human) or ab,tio(patient[*1]))
#29	MJMESH.EXACT("Parkinson Disease") OR MJEMB.EXACT("Parkinson disease") OR MJSUB("parkinson disease" OR "parkinson's disease")
#30	s28 and s29

Supplementary Table 2 Inconsistency model results [1]

A. Off time

Treatments		Consistency model		Inconsistency model	
		Mean	95% CrI	Mean	95% CrI
LCIG	BMT	2.253	(1.323, 3.185)	1.312	(-0.041, 2.662)
LCIG	CSAI	1.352	(0.111, 2.597)	2.183	(0.487, 3.880)
LCIG	DBS	-0.095	(-0.977, 0.791)	0.228	(-0.864, 1.324)
BMT	CSAI	-0.902	(-1.883, 0.081)	-1.893	(-3.159, -0.626)
BMT	DBS	-2.348	(-3.035, -1.662)	-2.501	(-3.248, -1.755)
CSAI	DBS	-1.446	(-2.606, -0.289)	0.314	(-195.3, 195.8)
Posterior mean of residual difference		19.1		13.1	
DIC		28.5		24.5	

Although the inconsistency model has a lower posterior mean of the residual difference and hence is a better fit to the data, the difference in DIC between the two models is less than 5. Note that a difference in DIC over 5 is important to choose one model over the other [1]. In addition, the 95% credible intervals from the two models overlap for all comparisons.

B. PDQ

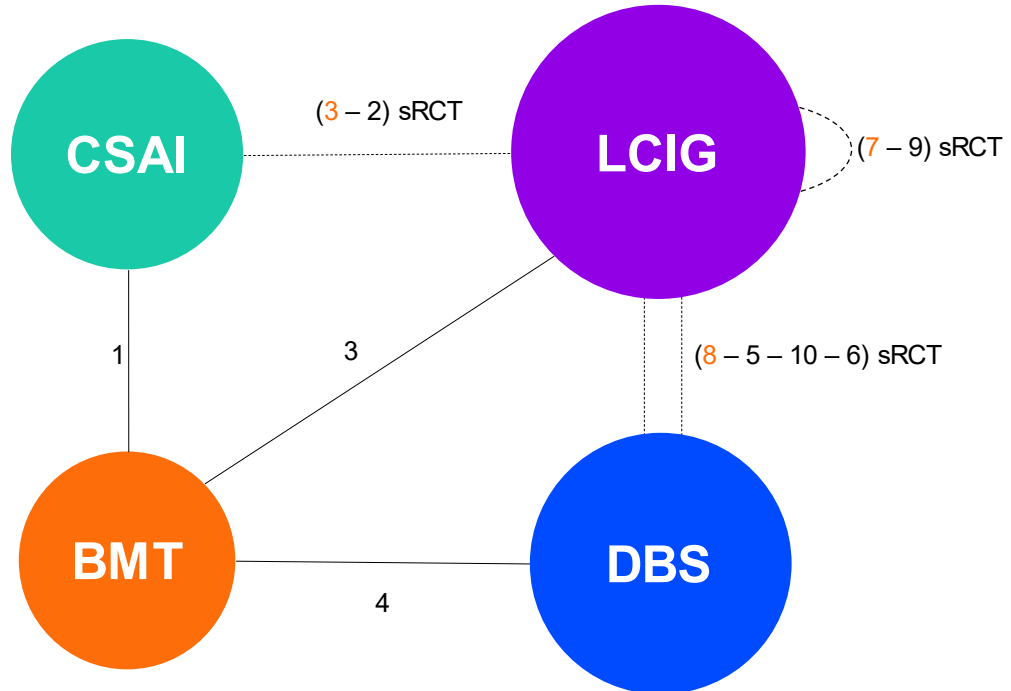
Treatments		Consistency model		Inconsistency model	
		Mean	95% CrI	Mean	95% CrI
LCIG	BMT	7.482	(4.809, 10.150)	4.134	(-0.633, 8.915)
LCIG	CSAI	4.094	(1.647, 6.534)	3.915	(1.285, 6.551)
LCIG	DBS	0.011	(-2.233, 2.251)	0.477	(-1.902, 2.861)
BMT	CSAI	-3.388	(-6.447, -0.332)	-2.481	(-7.620, 2.663)
BMT	DBS	-7.472	(-9.329, -5.614)	-8.483	(-10.61, 6.353)
CSAI	DBS	-4.083	(-6.949, -1.215)	0.314	(-195.3, 195.8)
Posterior mean of residual difference		48.2		46.4	
DIC		122.9		123.1	

Although the inconsistency model has a lower posterior mean of the residual difference and hence is a better fit to the data, the difference in DIC between the two models is less than 1. Note that a difference in DIC over 5 is important to choose one model over the other [1]. In addition, the 95% credible intervals from the two models overlap for all comparisons.

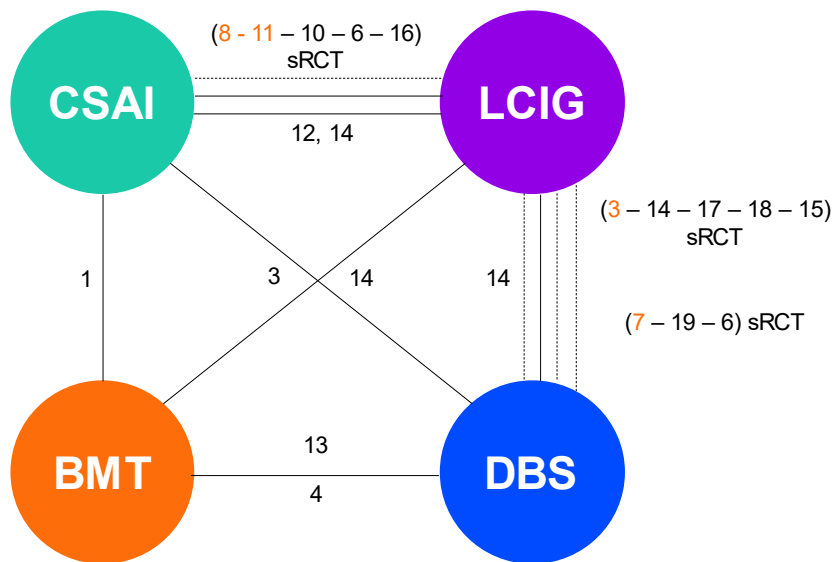
BMT, best medical therapy; CrI, credible intervals; CSAI, continuous subcutaneous apomorphine infusion; DBS, deep brain stimulation; DIC, deviance information criterion; LCIG, levodopa/carbidopa intestinal gel

Supplementary Fig 1 Networks after MAIC. (a) for off-time [2-11]; (b) for PDQ-8/PDQ-39 [2, 4, 5, 7-9, 11-20]

a



b



Orange text = individual patient data study. Black text = aggregate data study. Solid line = existing study. Dashed line = simulated study (sRCT). Numbers relate to reference list.
BMT, best medical therapy; DBS, deep brain stimulation; CSAI, continuous subcutaneous apomorphine infusion; LCIG, levodopa/carbidopa intestinal gel; sRCT, simulated randomized controlled study

Supplementary Fig 2 Risk of bias assessment of RCTs [2, 4, 5, 14, 21]

	Studies			
	Olanow et al 2014 [3]	Deuschl et al 2006 [13]	Katzenschlager et al 2018 [1]	Weaver et al 2009 [4]
Selection bias <i>Random sequence generation</i>	+	+	+	+
Selection bias <i>Allocation concealment</i>	+	X	+	?
Performance bias <i>Blinding of participants and personnel</i>	+	+	+	+
Detection bias <i>Blinding of outcome assessment</i>	?	X	+	+
Attrition bias <i>Incomplete outcome data</i>	+	+	X	+
Reporting bias <i>Selective reporting</i>	+	+	X	+
Other bias^a <i>Other sources of bias</i>	X	+	+	+
OVERALL RoB ASSESSMENT	High	High	High	Some concerns

RoB, risk of bias. RCT, randomized controlled trial.

























^aOther sources of bias that were considered included whether the study had an intention-to-treat analysis, and if so, whether this was appropriate and whether appropriate methods were used to account for missing data.

Supplementary Fig 3 Risk of bias assessment of non-randomized cohort studies [13, 15, 22]

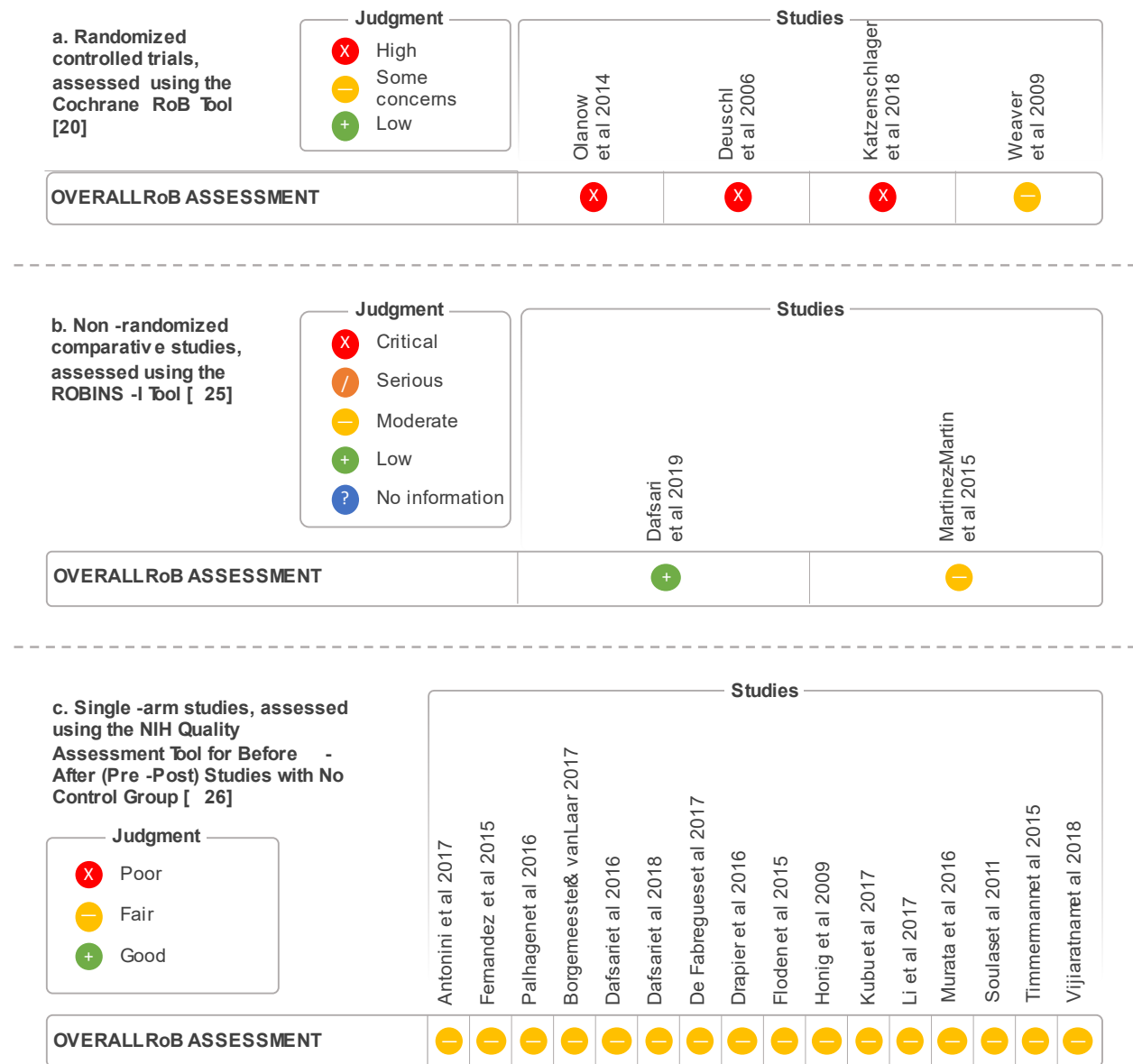
Judgment	Studies	
	Dafsaari et al 2019 [30]	Martinez-Martin et al 2015 [38]
Critical		
Serious		
Moderate		
Low		
No information		
Bias due to confounding		
Bias in selection of participants into the study		
Bias in classification of interventions		
Bias due to deviations from intended interventions		
Bias due to missing data		
Bias in measurement of outcomes		
Bias in selection of the reported result		
OVERALL RoB ASSESSMENT		

RoB, risk of bias.

Supplementary Fig 4 Risk of bias assessment of single-arm studies [3, 6-12, 16-20, 23-26]

	Judgment				Studies																					
	 Poor	 Fair	 Good		N	Y	CD	NA	NR	Antonini et al 2017 [22]	Fernandez et al 2015 [20]	Palhagen et al 2016 [21]	Borgemeester & van Laar 2017 [28]	Dafsari et al 2016 [43]	Dafsari et al 2018 [29]	De Fabregues et al 2017 [31]	Drapier et al 2016 [33]	Floden et al 2015 [34]	Honig et al 2009 [35]	Kubu et al 2017 [36]	Li et al 2017 [37]	Murata et al 2016 [39]	Soulas et al 2011 [40]	Timmermann et al 2015 [41]	Vijjaratanam et al 2018 [42]	
Was the study question or objective clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were eligibility/selection criteria for the study population prespecified and clearly described?	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were all eligible participants that met the prespecified entry criteria enrolled?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the sample size sufficiently large to provide confidence in the findings?	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the test/service/intervention clearly described and delivered consistently across the study population?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the people assessing the outcomes blinded to the participants' exposures/interventions?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Y	CD	CD	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p-values for pre-to-post changes?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
OVERALL RoB ASSESSMENT																										

Supplementary Fig 5 Risk of bias assessment of: (a) RCTs; (b) non-randomized controlled trials; and (c) single-arm studies [2-22, 24-26]



RoB, risk of bias. RCT, randomized controlled trial.

References for supplementary file

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