

SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

ltem #	Section/Subsection/Item	Description	Check for approval
	A. General		
1.	Title of the review	Remyelination promoting therapies in multiple sclerosis animal models: a systematic review and meta-analysis	
2.	Authors (names, affiliations, contributions)	Benjamin Victor Ineichen ^{1, 2} Martin Hlavica ³ Marc Schneider ¹ Nicolas Good ¹ Andrin Good ¹ Lisa Baumgartner ¹ Gianluca Galeno ¹ Carlijn Hooijmans ⁴ Rob DeVries ⁴ ¹ University and ETH Zürich, Brain Research Institute, Switzerland ² University Hospital Zurich, Department of Neurology, Switzerland ³ Cantonal Hospital St. Gallen, Department of Neurosurgery, Switzerland ⁴ SYRCLE at Central Animal Laboratory, Radboud University Medical Center, Nijmegen, the Netherlands	
3.	Other contributors (names, affiliations, contributions)	To be determined	
Δ	Contact person + e-mail address	ineichen@protonmail.ch	
5.	Funding sources/sponsors	Swiss Multiple Sclerosis Society, Hartmann-Müller- Foundation, Desirée-and-Niels-Yde-Foundation, Swiss National Science Foundation	
6.	Conflicts of interest	The authors declare no conflict of interest	
7.	Date and location of protocol registration		
8.	Registration number (if applicable)		
9.	Stage of review at time of registration	Database search and abstract sorting completed, data extraction started	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Multiple sclerosis (MS) is a chronic neuro-inflammatory disease mainly starting in young ages. Whereas some immune system modulating therapies are available for the early disease stages in which immune cells infiltrate the central nervous system (CNS), no therapies exist for the progressive phase, defined by chronic demyelination and neurodegeneration. Therefore, finding therapies which promote myelin repair is top priority in neurological research. The four most commonly used animal models to	

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Image: set in the set in			assess candidate drugs for their purely remyelinating
and anti-galactocerebroside antibodies/complement. However, racking overview about all assessed approaches in these models to enhance remyelination is very challenging. Hence, we aim at summarizing these potential interventions by this systematic review. Moreover, we are aiming at performing a meta-analysis on therapies which have been assessed more than once to estimate their efficacy. Finally, we plan to correlate these results with the outcome of clinical trials in human patients to determine parameters for succesful clinical translation. 11. Specify the disease/health problem of interest Multiple sclerosis 12. Specify the disease/health problem of interventions which aim at improving remyelination Multiple sclerosis 13. Specify the control population Interventions which aim at improving remyelination 14. Specify the control population No interventions which aim at improving remyelination 14. Specify the outcome measures •Remyelination outcomes such as electron microscopy/light microscopy on analysis of remyelinated axons, optical density in myelin stainings, demyelinated area in myelin stains, etc. 15. Specify the outcome measures 1.) What is the current evidence for the efficacy of remyelinating interventions who and anti- galactocerbroside antibodies/complement? 16. State your research question (based on items 11-15) 1.) What is the current evidence for the efficacy of remyelinating interventions the MS animal models lysolecithin, ethidium bromide, cupricone, and anti-			properties are lysolecithin, ethidium bromide, cuprizone,
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		,	XOther, namely: go3R, BIOSIS

18.	Define electronic search strategies (<i>e.g.</i> use the <u>step by step search</u> <u>guide¹⁵</u> and animal search filters ^{20, 21})	Consider supplementary search strings	
19.	Identify other sources for study identification	XReference lists of included studies XReference lists of relevant reviews	
20.	Define search strategy for these other sources	Examination of reference lists from relevant articles	
	Study selection		
21.	Define screening phases (<i>e.g.</i> pre- screening based on title/abstract, full text screening, both)	 Pre-screening based on title and abstract Full-text screening of the eligible articles, since a few thousand articles are available, full-text screening will be focused on abstract, method section and figures. In unclear cases, other parts will be considered as well. 	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	 2 independent reviewers per abstract, abstracts/articles on which the reviewers disagree articles will be included in the full-text screening (over-inclusion approach) 2 independent observers per article. Differences will be solved through discussion or by consulting a third investigator. 	
	Define all inclusion and exclusion criter	ia based on:	
23.	Type of study (design)	Inclusion criteria: Original works (including conference abstracts); use of an adequate control group (Vehicle only treatment) Exclusion criteria: Studies which did not investigate a therapy in these MS models will be excluded; a therapy is defined as a directly or indirectly and exogenous to the animal applied substance or intervention (e.g. studies which only investigate pathogenic aspects of MS or studies which only use transgenic approaches will be excluded). Reviews will be excluded but retained as a source for potential studies and for discussion.	
24.	Type of animals/population (<i>e.g.</i> age, gender, disease model)	Inclusion criteria: all sexes, ages, rat and mice strains and one or more of the four types of models mentioned above Exclusion criteria: Studies where only transgenic animals were used, studies in which MS disease models are combined with other disease models (e.g. diabetic rats), in vitro approaches only (e.g. cerebellar rat slice cultures), mainly inflammatory MS animal models (e.g. EAE, TMEV)	
25.	Type of intervention (<i>e.g.</i> dosage, timing, frequency)	Inclusion criteria: all therapy regimens will be included (therapeutic, prophylactic, combined approaches) and therapies which aim at improving remyelination (histology/electron microscopy and/or myelinating or pre- myelinating cell counts (oligodendrocytes and OPCs))	

		Exclusion criteria: application (e.g. in case of proteins) via
		viral vectors (potential off target effects)
26	Outcome measures	Inclusion criteria: outcome measures related to
20.	Outcome measures	remyelination or (pre-)myelinating cell counts
27.	Language restrictions	Inclusion criteria: all languages
20	Publication data restrictions	Inclusion criteria: all publication dates
20.		Exclusion criteria: none
20	Other	Inclusion criteria: none
25.		Exclusion criteria: none
		Selection phase: screening of abstracts and full-text
		1. Non-original article
		2. No therapy tested
		3. In vitro only
		4. Only transgenic animals used
		5. None of above mentioned animal models used
	Sort and prioritize your exclusion	
30.	criteria per selection phase	Exclusion criteria for the meta-analysis: full-text screening
		1. No data on remyelination
		2. No reporting of quantitative data
		3. Unly Gratio as remyelihation readout
		4. No reporting of animal numbers or statistical
		from studies in which no animal numbers and/or
		statistical variability are reported)
	Study characteristics to be extracted (fr	ar assossment of external validity, reporting quality)
31	Study (D (e g authors year)	Authors year title journal language
51.	Study design characteristics (e a	
32.	experimental groups, number of	Number of animals per group
52.	animals)	
	Animal model characteristics (e.g.	
33.	species, gender, disease induction)	Species, strain, sex, type of model
	Intervention characteristics (<i>e.g.</i>	Therapeutic/prophylactic/combined application regimen +
34.		molecule used, dose, administration route etc.
	intervention, timing, duration)	
		All MS-related outcomes will be used.
	Outcome measures	
		For remyelination outcomes, following extraction priority
		list is used:
		1.) Electron microscopy: amount of remyelinated axons
		between treatment and control group(s)
		(disproportionally thinly myelinated axons)
		2.) Toluidine blue/semithin section: amount of
35.		remyelinated axons between treatment and control
		group(s) (disproportionally thinly myelinated axons)
		3.) Other stainings (e.g. MBP staining, sudan black
		staining): amount of remyelinated axons between
		treatment and control group(s) (disproportionally thinly
		myelinated axons)
		4.) Other stainings (e.g. WBP, LFB, DIack gold, eriochrome,
1		and others): lesion volume/area between treatment and
		a control group (c)

		 5.) Magnetic resonance imaging (MRI): lesion volume/area 6.) Other stainings (e.g. MBP, LFB, black gold, eriochrome, and others): optical density within lesion between treatment and control group(s) 	
		For oligodendrocyte and OPC counts, stainings will be extracted with no priority	
36.	Other (<i>e.g.</i> drop-outs)		
	Assessment risk of bias (internal validit	y) or study quality	
37.	Specify (a) the number of reviewers assessing the risk of bias/study quality in each study and (b) how discrepancies will be resolved	2	
38.	Define criteria to assess (a) the internal validity of included studies (<i>e.g.</i> selection, performance, detection and attrition bias) and/or (b) other study quality measures (<i>e.g.</i> reporting quality, power)	By use of SYRCLE's Risk of Bias tool, adapted as follows: addition of one additional reporting item: is there reporting of randomization at any step?	
	Collection of outcome data		
39.	For each outcome measure, define the type of data to be extracted (<i>e.g.</i> continuous/dichotomous, unit of measurement)	For quantitative synthesis: continuous measurements will be extracted	
40.	Methods for data extraction/retrieval (<i>e.g.</i> first extraction from graphs using a digital screen ruler, then contacting authors)	First extraction from numbers in text or tables, second numbers from graphs using universal desktop ruler software (http://avpsoft.com/products/udruler/) by two independent reviewers. (If data could not be extracted from text or figures authors will be contacted via e-mail (max. 1 e-mail)).	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	2, by discussion, ultimately by a third reviewer	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (<i>e.g.</i> descriptive summary, meta-analysis)	If possible, meta-analysis with subgroup analysis and sensitivity analysis for all outcome measures. Following meta-analyses will be performed: 1.) On the remyelination outcome (remyelination per se, measured by electron microscopy/histology). Since disproportionally thinly myelinated axons are the gold standard of measuring remyelination and therefore the most robust outcome measure, a second meta-analysis only including studies using this outcome readout will be performed (1.) to 3.) from the list from point 35). 2.) On oligodendrocyte cell counts. 3.) On OPC counts. In case numerical outcomes were quantified using different scales, mean and standard deviation will be	

		qualitative/descriptive analysis	
		Exclusion criteria for quantitative synthesis: Papers only reporting qualitative data on remyelination, papers with only G ratio as quantitative remyelination readout due to the limited relative effect size (due to the differences in potential remyelination readout)	
	Specify (per outcome measure) how it		
43.	will be decided whether a meta-	See 42.	
	analysis will be performed		
	If a meta-analysis seems feasible/sensi	ble, specify (for each outcome measure):	
	The effect measure to be used (e.g.	Standardized mean differences (SMD). If possible, we will	
44.	mean difference, standardized mean	do a sensitivity analysis in which we only include the	
	difference, risk ratio, odds ratio)	studies for which we can calculate an NMD (normalized	
	The statistical model of analysis (a.g.	mean difference)	
45.	random or fixed effects model)	Random effects model, Forest-plot for visualization	
46	The statistical methods to assess	1 ²	
	heterogeneity (<i>e.g.</i> I ² , Q)		
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	Subgroup analysis will only be performed in therapies which have been tested 4 or more times per outcome measure (remyelination, oligodendrocyte cell count or OPC count): •Species (rats vs. mice) •Sex •Prophylactic vs. therapeutic therapy regimen •MS animal model •Type of remyelination outcome/intervention	
48.	Any sensitivity analyses you propose to perform	To be determined	
49.	Other details meta-analysis (<i>e.g.</i> correction for multiple testing, correction for multiple use of control group)	To be determined	
50.	The method for assessment of publication bias	Funnel plots or Eggers test in case of small study effects (n-based estimate of precision for your funnel plot)	
Final approval by (names, affiliations): Benjamin Victor Ineichen Brain Research Institute Date: 24.02.2017 Switzerland Switzerland			.02.2017