SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

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Item #	Section/Subsection/Item	Description	Check for approval
	A. General		
1.	Title of the review	Assessment of lower urinary tract function in rodents: a systematic review for consensus statement on terminology and normal values	
2.	Authors (names, affiliations, contributions)	**Marc P. Schneider**, University and ETH of Zürich study design, study selection, data extraction, data analysis, RoB assessment, manuscript writing, manuscript approval **Miriam Koschorke**, University of Zürich study selection, data extraction, RoB assessment, manuscript approval **Andrea Sartori**, University of Zürich data extraction, RoB assessment, manuscript approval **Jure Tornic**, University of Zürich data extraction, RoB assessment, manuscript approval **Selina Moors**, University of Zürich data extraction, RoB assessment, manuscript approval **Claudius Füllhase**, Rostock University Hospital study design, manuscript approval **Francis "Monty" Hughes Jr**, Duke University Medical Center study design, manuscript approval **J. Todd Purves**, Duke University Medical Center study design, manuscript approval **Karl-Erik Andersson** study design, manuscript approval **Lucas M. Bachmann**, Medignition Inc. study design, data analysis, manuscript writing, manuscript approval **Thomas M. Kessler**, University of Zürich study design, study selection, data extraction, data analysis, RoB assessment, manuscript writing, manuscript approval	
3.	Other contributors (names,	The following contributors have critically revised the study	

	affiliations, contributions)	protocol: Ana Coelho, Hospital de S. Joao and Faculty of Medicine of Porto Jacques Corcos, Jewish General Hospital Montreal Francisco Cruz, Hospital de S. Joao and Faculty of Medicine of Porto William C. de Groat, University of Pittsburgh Dirk de Ridder, University Hospital Leuven Anne K. Engmann, University and ETH of Zürich Benjamin V. Ineichen, University and ETH of Zürich Martin Flück, University of Zürich Matthew O. Fraser, Duke University Medical Center Jerzy Gajewski, Dalhousie University Halifax Petter Hedlund, Linköping University Ulrich Mehnert, University of Zürich Martin E. Schwab, University and ETH of Zürich Jan Schwab, Ohio State University Karl-Dietrich Sievert, University of Salzburg Roberto Soler, University of São Paulo Tomi Streng, University of Turku Marco Tedaldi, University and ETH of Zürich Gommert A. van Koeveringe, University Hospital Maastricht Naoki Yoshimura, University of Pittsburgh	
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5.	Funding sources/sponsors	Swiss Continence Foundation www.swisscontinencefoundation.ch	
6.	Conflicts of interest	The authors report no conflicts of interest	
7.	Date and location of protocol registration	11th of November 2015	
8.	Registration number (if applicable)	NA	
9.	Stage of review at time of registration	Systematic search and abstract-screening completed, full text extraction started	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Rodents, especially mice and rats, are the most frequently used laboratory animals for lower urinary tract function research. However, there are no generally agreed normal values. Additionally there are many different methods in use, each with advantages, disadvantages and limitations. Nevertheless there is no consensus statement with recommendations on the methods' strength and weaknesses. To come up with recommendations, the first step is to summarize all the available evidence of functional lower urinary tract assessment in rodents, what will be the aim of this systematic review. A big problem of the field is the non-standardized terminology, what highly hampers the comparability of different studies. Therefore we also aim to address this issue by word frequency analysis and come up with a	

		recommendation of terminology for functional lower urinary tract assessment. To increase the translational value of our field, we are in close cooperation with the International Continence Society (ICS) and we will match the functional lower urinary tract terminology in rodents as fare as it makes sense and is possible to the terminology used in humans. We additionally aim to identify potential confounders and risk for bias to come up with recommendations on regulations of study designs, bias control systems, and systems for evaluation of validity and predictive value to improve translation from preclinical models to humans.	
	Research question		
11.	Specify the disease/health problem of interest	Lower urinary tract function assessment in rodents	
12.	Specify the population/species studied	Rodents	
13.	Specify the intervention/exposure	Any kind of lower urinary tract function assessment in rodents	
14.	Specify the control population	No intervention or placebo intervention (degree of severity will be assessed i.e. sham surgery and only interventions with very low risk of biasing the lower urinary tract function will be included, i.e. salin injection or comparable intervention)	
15.	Specify the outcome measures	Primary outcomes: Lower urinary tract function parameters (such as detrusor pressure, detrusor overactivity, compliance, number of voids, voided volume, post void residual, voiding efficiency etc.) Secondary outcomes: Terms and definitions used in lower urinary tract function assessment	
16.	State your research question (based on items 11-15)	1. To summarize all evidence on lower urinary tract function assessment in rodents 2. To compare lower urinary tract parameters in healthy rodents versus rodents with different disorders (i.e. spinal cord injury; multiple sclerosis, cerebral infarction or Parkinson's disease like disorders; outflow obstruction; inflammation etc.) and to define normal values for lower urinary tract parameters 3. To identify advantages and disadvantages of different lower urinary tract function assessments and to give some consensus recommendations on which technique should be used in which situation 4. To give recommendations on technical aspects of	

		urodynamics in rodents (such as anesthesia; surgical techniques; urodynamic setup; equipment and tools; technique (infusion rate; catheterization; duration of urodynamics; data analysis and data presentation) 5. To summarize terms and definitions used in lower urinary tract function assessment in rodents 6. To standardize terminology of lower urinary tract function in rodents considering the International Continence Society (ICS) terminology in humans 7. Recommendations on regulations of study designs, bias control systems, and systems for evaluation of validity and predictive value to improve translation from preclinical models to humans	
	C. Methods		
	Search and study identification		
17.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	The search was performed in EMBASE, MEDLINE, SCOPUS and PubMed. Searched keywords include the following: • Urodynamics or bladder pressure measurement or cystometry or cystomanometry or urethral pressure measurement or lower urinary tract function or bladder function or electromyography of pelvic floor or electromyography of external urethral sphincter or metabolic cage or voiding volume or investigation of urinary storage and voiding function or voiding pattern AND • Rodent or rat or mice or Guinea pig The search will not be limited by language or publication year.	
18.	Define electronic search strategies (*e.g.* use the step by step search guide[15] and animal search filters[20, 21])	When available, please add a supplementary file containing your search strategy: [Embase Search Strategy - Systematic Review of lower urinary tract function in rodents.pdf]	
19.	Identify other sources for study identification	Other search strategies will include citation searching and examination of reference lists from relevant articles.	
20.	Define search strategy for these other sources	Please see Point 19.	
	Study selection		

21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	Phase 1: screening of title and abstract to remove references with no relation at all to the review topic Phase 2: final inclusion or exclusion based on full-text screening of title and abstract	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	Phase 1: all abstracts and titles were assessed independently by two reviewers (MPS and MK) and disagreements were resolved by a third reviewer (TMK). Phase 2: each reference is assessed full-text by one to two reviewers from the review team (MPS, MK, AS, JT, SM, TMK). Disagreements are resolved through discussion with another reviewer.	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criteria: studies with a control group Exclusion criteria: case reports	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: Rodents, any age or sex Exclusion criteria:Non - rodents	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: Not applicable (since we are mainly interested in the control groups) Exclusion criteria: Not applicable	
26.	Outcome measures	Inclusion criteria: : Any outcome reporting on any type of lower urinary tract function assessment Exclusion criteria: No outcome reporting on any type of lower urinary tract function assessment	
27.	Language restrictions	Inclusion criteria: any language Exclusion criteria: No language restriction	
28.	Publication date restrictions	Inclusion criteria: any date Exclusion criteria: No date restriction	
29.	Other	Inclusion criteria: Exclusion criteria:	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase 1: 1. Article without original data (e.g. review, editorial) 2. Not an in vivo, rodent animal study 3. No lower urinary tract function assessment Selection phase 2: 1. Article without original data (e.g. review, editorial) 2. Not an in vivo, rodent animal study 3. No lower urinary tract function assessment 4. No relevant outcome measures 5. No control group or light sham intervention group 7. Article not retrievable	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	Author, year of publication	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	Treatment or pathology model used Additional findings to urodynamics Study type	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	Supplier of the animals Total Number of animals	

		Animal species used Strain Age Weight Gender Sham operated Type of sham surgery Injected placebo solution (saline, vehicle, control) Severity of sham surgery Pathology model used Normal or inverted housing cycle	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	Measurement Urodynamic Techniques Type of restrainers / freely moving Urodynamic assessement How many days after catheter implantation Measurement under anaesthesia Drug used for anaesthesia Dose in mg / kg body weight EMG of the external uretheral sphincter (EUS) Technical tool used to assess void volume or flow Infusion speed Infusion liquid Diameter of Catheter (Tubing) and Material Duration of measurement	
35.	Outcome measures	Basal Pressure Premicturition volume (=Micturition-Threshold volume) Premicturition pressure (=Micturition-Threshold Pressure) Void Volume Bladder capacity Post void residual volume Micturition time Maximum bladder pressure during storage time Maximum bladder pressure during voiding time Maximal flow rate Micturition interval Micturition frequency Compliance	
36.	Other (*e.g.* drop-outs)		
	Assessment risk of bias (internal validity) 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	Each reference is assessed full-text by one to two reviewers from the review team (MPS, MK, AS, JT, SM, TMK). Disagreements are resolved through discussion with another reviewer.	
38.	Define criteria to assess (a) the internal validity of included studies (*e.g.* selection, performance, detection and attrition bias) and/or (b) other study quality measures (*e.g.* reporting quality, power)	☐By use of SYRCLE's Risk of Bias tool[4] X By use of SYRCLE's Risk of Bias tool, adapted as follows: Random sequence generation, attrition bias, Blinding of personel, Blinding of outcome assessement (detection bias), Animal license aprooved by local ethical comity, Standard housing reported, Methodes sufficient described	

		Additionally we will use an extra item to assess the risk of findings being explained by confounding. As the 6 most important potential confounders for efficacy/safety, we identified animal strain, weight, gender, medication, type of therapy, duration from implantation of catheter until measurement and if the measurements were performed awake or under anaesthesia. For each study, we will assess whether each prognostic confounder was considered and whether, if necessary, the confounder was controlled for in analysis.	
	Collection of outcome data		
39.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/dichotomous, unit of measurement)	The goal is to have all urodynamic results or outcomes and it might be that we did not yet include all possible outcomes (or better it is likely). Thereby any new outcome will be added and for that we will add four new columns (one for the value and 3 for SD, SEM and CI) to have a marker for the variability. Different units: i.e. pressure can be plotted as mmHg or as cmH2O (1mmHg is 1.36 cmH2O) please calculate the cmH2O if they report mmHg by multiplication with 1.36. The unit to use is always in the [] in line number 2 of the excel sheet i.e. [mL] = millilitres. If we have there [seconds], and they report times in minutes, please calculate to seconds.	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	1. Numerical data from text or tables. 2. If data are only presented graphically, graphs will be measured using a digital screen ruler . 3. In case of missing data, we will contact authors in an attempt to retrieve additional information. In case of no response within three weeks including a reminder, the study will be excluded from analysis.	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	Each reference is assessed full-text by one to two reviewers from the review team (MPS, MK, AS, JT, SM, TMK). Disagreements are resolved through discussion with another reviewer.	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	Individual study results will be summarized with the mean and standard deviation in each group (for numerical outcomes) or percentages (dichotomous outcomes). If numerical outcomes were quantified with different scales, standardized mean differences will be calculated.	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	Meta-analysis: Heterogeneity (i.e. differences between studies) will be assessed graphically using forest plots and statistically using I-squared to aid in decisions on how to proceed with quantitative synthesis. The I-squared is the proportion of total variability explained by heterogeneity. This formal statistical analysis examines whether the observed variation in study results is compatible with the variation expected by chance alone. An I-squared value of 0 percent indicates no heterogeneity whereas values above 50 percent arbitrarily indicate moderate to high heterogeneity. Exploration of the causes of heterogeneity is planned using variation in features of the population	

		(inclusion and exclusion criteria), intervention(s), outcome (clinical heterogeneity) and study quality (methodological heterogeneity). If appropriate, we plan to perform fixed effects meta-analysis if heterogeneity is low (I-squared below 25 percent). Random effects pooling will be performed if moderate unexplained heterogeneity is present (I-squared below 50 percent). However, these summaries will be interpreted very cautiously. No pooling will be undertaken in the presence of significant source heterogeneity.	
	If a meta-analysis seems feasible/sensible, specify (for each outcome measure):		
44.	The effect measure to be used (*e.g.* mean difference, standardized mean difference, risk ratio, odds ratio)	To be determined, Please see also point 43.	
45.	The statistical model of analysis (*e.g.* random or fixed effects model)	Please see point 43.	
46.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	Please see point 43.	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	Supplier of the animals Animal species used Strain Age Weight Gender Sham operation Time between implantation of catheter and measurement Whether the measurements were performed awake or under anaesthesia	
48.	Any sensitivity analyses you propose to perform	To be determined	
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	To be determined if needed. (i.e. Holm-Bonferroni correction for testing multiple subgroups)	
50.	The method for assessment of publication bias	We will use funnel plots and visual analysis of these plots for outcome measures containing >20 studies. Egger's test will be used for small study effects for outcome measures containing >20 studies.	

Final approval by (names, affiliations):
On behalf of all co-authors, Date: 11-11-2015
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