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	A systematic review on the implementation and reporting of refinements in mouse telemetry implantation surgery using electrocardiography (ECG) recording devices.	
2.	Authors (names, affiliations, contributions)	• Alexandra Gkrouzoudi (DVM, Lab. Animal Facility Designated Veterinarian, Lab. of Anatomy, Histology and Embryology, School of Veterinary Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki): design study, data extraction and analysis, writing manuscript. • Paulin Jirkof (PhD, Dept. Animal Welfare and 3R, University of Zurich): design study, solving of discrepancies during selection and extraction process, writing manuscript. • Anastasia Tsingotjidou (Asst. Professor Lab. of Anatomy, Histology and Embryology, School of Veterinary Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki): data extraction and analysis, writing of manuscript.	
3.	Other contributors (names, affiliations, contributions)	M.Sc. Laboratory Animal Science, International Academy, RWTH Aachen University	
4.	Contact person + e-mail address	Contact person: Alexandra Gkrouzoudi E-mail assress: alexandra.gkrouzoudi@rwth-aachen.de or gkrouzoudi@gmail.com	

5.	Funding sources/sponsors	-	
6.	Conflicts of interest	No conflicts of interests	
7.	Date and location of protocol registration	-	
8.	Registration number (if applicable)		
9.	Stage of review at time of registration	The review will start at the time of the registration	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Telemetric monitoring is used in many scientific set ups including the monitoring of discomfort. Miniature implantable radiotelemetric devices offer the possibility of long-term, hands-off measurement of body temperature, motor activity, biopotentials (EEG, ECG, electromyogram) and blood pressure in conscious, freely moving animals throughout the circadian cycle. Since changes in body temperature, motor activity, heart rate and blood pressure are well-characterized responses to stress [1], telemetry offers advantages such as the refinement in animal procedures by permitting virtually unrestricted continuous data collection, the reduction in animal usage and the elimination of confounding stress effects introduced by handling, restraint, and anesthesia for certain data acquisition. On the other hand, the main disadvantages are the requirement of an invasive surgical procedure for the implantation of the transmitter device, which impose welfare concerns. The surgery requires a skilled surgeon (especially for mice) and rodents need at least 7-10 days to recover fully after surgery [2, 3, 4]. State of the art, aseptic rodent surgery is therefore an important component of these procedures and several refinements have been proposed in the past. Additionally, the following factors have to be taken in consideration regarding the effects a telemetry device might have on the animal. First is the body to transmitter ratio where it may put a burden on mice since it may represent 2-10% of its body mass, possibly decreasing body weight, grooming and motor activity for several days post surgically [4, 5, 6, 7]. Of course, the modern telemetric implants have been miniaturized at a point that this burden can be surpassed as much as possible. Another effect of telemetry is the disruption of circadian body temperature and motor activity rhythmicity levels following surgery, but after a sufficient recovery period, no influence of the transmitter can be detected [8]. An additional stressor can be the fact	

		that single housing is used by most studies to minimize signal interference. Lastly, the effects of anaesthesia and analgesia used for the surgery have to be considered. The postoperative effects of analgesics involve more than just pain relief. Commonly used analgesics are known to modify locomotor activity [9], food consumption [10], fluctuations in body weight [11] and hemodynamic factors [9, 12]. In this systematic review, we will provide an overview of all reported procedures in mouse studies until 31.12.2019 using surgery that involves the placing of ECG recording telemetry devices and an overview of the methodological quality of all these studies. Furthermore, we will investigate and report the trends in refinements observed until 31.12.2019. Additionally, a comparison will be made between the periods before and after 2010 (when the ARRIVE Guidelines were developed, as a tool to evaluate reporting quality). Lastly, we will investigate the different factors affecting the welfare of the animals after the implantation surgery. The ECG telemetry implantation surgery was chosen among other types of existing telemetric measurements (as described above) because of its potential increased severity (especially when the device is implanted in the intraperitoneal region of the animal). This way we will achieve to showcase possible refinements that have been applied during the course of time in the field of biotelemetry, and more specifically when ECG recording devices are utilized.	
	Research question		
11.	Specify the disease/health problem of interest	Animal welfare, refinement and scientific quality	
12.	Specify the population/species studied	Adult mice (>6 weeks old) of all sexes and strains	
13.	Specify the intervention/exposure	Implantation of ECG recording telemetry device	
14.	Specify the control population	Results will be descriptive, studies before and after 2010 will be compared in regard to their use of refinement and reporting quality	
15.	Specify the outcome measures	Use of refinement, reporting quality	
16.	State your research question (based on items 11-15)	Is there an increased uptake of refinement measures and reporting standards since 2010?	

	C. Methods		
	Search and study identification		
17.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	**X** MEDLINE via PubMed **X** Web of Science ☐SCOPUS **X** EMBASE ☐Other, namely: ☐Specific journal(s), namely:	
18.	Define electronic search strategies (*e.g.* use the step by step search guide[15] and animal search filters[20, 21])	Attached supplementary file: Search Strategy_ECG Telemetry_PubMed_WoS_Embase_29_2_2020	
19.	Identify other sources for study identification	**X** Reference lists of included studies ☐Books **X** Reference lists of relevant reviews ☐Conference proceedings, namely: ☐Contacting authors/ organisations, namely: ☐Other, namely:	
20.	Define search strategy for these other sources	-	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	1) pre-screening based on title and abstract 2) full-text screening of the eligible articles	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	Each phase: 2 independent observers (AG, AT) per article. Differences will be solved through discussion or by consulting a third investigator (PJ)	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	**Inclusion criteria:** Every type of study design is of interest **Exclusion criteria:** None	
24.	Type of animals/population (*e.g.* age, gender, disease model)	**Inclusion criteria:** Any study that uses adult mice (>6 weeks old, of any strain and sex) **Exclusion criteria:** 1. Any study that does not use adult mice (>6 weeks old) 2. Any study that uses any other species besides adult mice (>6 weeks old, of any strain and sex)	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	**Inclusion criteria:**	

		Studies that use ECG recording implantable telemetry **<u>Exclusion criteria:</u>** 1. Any study that does not use ECG recording telemetry devices 2. Any study using external telemetry (e.g. jackets)	
26.	Outcome measures	No inclusion or exclusion by outcome measures	
27.	Language restrictions	**<u>Inclusion criteria:</u>** Only English **<u>Exclusion criteria:</u>** Any other language besides English	
28.	Publication date restrictions	**<u>Inclusion criteria:</u>** All publications until 31.12.2019 **<u>Exclusion criteria:</u>** Any publication date after 31.12.2019	
29.	Publication type	**<u>Inclusion criteria:</u>** Primary/original studies **<u>Exclusion criteria:</u>** 1. Any studies that are not primary/original studies (e.g. reviews, conference proceedings) 2. No full papers (abstract, comment) 3. Data published in duplicate	
30.	Sort and prioritize your exclusion criteria per selection phase	**<u>Selection phase tiab screening:</u>** 1. Not a primary/original study 2. Review 3. No full paper (abstract, comment) 4. Data published in duplicate 5. Any other species besides mice 6. Any age <6 weeks old 7. Any study that does not use ECG recording telemetry devices 8. Any study using external telemetry (e.g. jackets) **<u>Selection phase full text screening:</u>** 1. Not a primary/original study 2. Any other species besides mice 3. Any age <6 weeks old 4. Any study using external telemetry (e.g. jackets)	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		

31.	Study ID (*e.g.* authors, year)	• Article title • Date • Authors • Journal name	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	• Field / Discipline • Number of animals per group (to assess the severity of the dropouts)	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	• Strain, sex, age, weight • Genetic modification • Health / Immune status	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	• Anesthesia used (type, dose, route) • Analgesia used (type, dose, route, duration), • Technique of implantation • Aseptic technique used • Mean surgery duration • Implantation site of device body • Device model/size/weight • Age at the time of device implantation • Recovery period after surgery and before study begins • Telemetric measurements (duration, frequency) • Refinement measures prior/during/after experiment (fluid therapy, soft food, warming, gentle handling, preconditioning, other)	
35.	Outcome measures	• Pain/Welfare assessment (score sheet or other method, which parameters were assessed) • Any description done by the author regarding the behavioural or physical change of the animals (e.g. aggressivity, self-mutilation etc) • Assessment of analgesic efficacy (if yes – was it effective) • Mortality (rate, reason) • Dropouts (number, reason)	
36.	Other (*e.g.* drop-outs)	• Type of housing (single/group/other, No. of cage companions) • Caging type (OHB, SPF housing, hygiene monitoring) • Diet (type, access) • Water quality (quality, access) • Bedding material	

		• Light/Dark cycle • Housing temperature and humidity • Environmental enrichments (wheel, nesting material, other) • Type of cage/environment during the animal recovery period after the implantation surgery and if any measures are being taken to reduce the severity of the recovery • Other measurements conducted with the same telemetry device (BP, HR, Tc, MA, etc.) • Simultaneous use of other implantable devices (mini-pumps, etc.) • Interventions other than the ECG telemetric measurements (type, duration, frequency) • Re-use of animals (if yes: field, severity, duration) • Internal validity/Types of observed bias (selection, performance, detection, attrition) • Reporting of ethical approval • Statistical analysis used (Were the statistical methods described? Was the sample size justified?) • Reporting quality (unchecked items from the ARRIVE Guidelines, besides ethical approval and statistical analysis) • Journal impact factor	
	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	a) 2 reviewers. The criteria will be independently assessed by AG and AT by using collectively predefined assessment criteria b) discrepancies will be resolved by discussion or by consulting a third investigator (PJ)	
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)	**X** By use of SYRCLE's Risk of Bias tool[4] ☐By use of SYRCLE's Risk of Bias tool, adapted as follows: ☐By use of CAMARADES' study quality checklist, e.g [22] ☐By use of CAMARADES' study quality checklist, adapted as follows: ☐Other criteria, namely:	
	Collection of outcome data		
39.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/dichotomous, unit of measurement)	Our outcome measures are diverse and mentioned under the extraction characteristics field.	

40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	We shall use text and graphs in order to collect the information we need.	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	a) Two reviewers (AG and AT) will extract all data b) discrepancies will be resolved by discussion or by consulting a third investigator (PJ)	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	Narrative synthesis will give an overview of study characteristics, refinement measures (types, frequency, effectiveness etc.) and quality of analysed studies (using the above described indicators). If possible, we will add a descriptive summary consisting of absolute/relative numbers in graphs.	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	-	
	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)	-	
45.	The statistical model of analysis (*e.g.* random or fixed effects model)	-	
46.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	-	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	-	
48.	Any sensitivity analyses you propose to perform	-	
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	-	
50.	The method for assessment of publication bias	-	

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