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	Quantification of translational success: rates of concordance between the results of animal experiments and human trials – A systematized review	
2.	Authors (names, affiliations, contributions)	Julia Menon Carien Kouwenaar Frans Stafleu Rob de Vries Merel Ritskes-Hoitinga Franck Meijboom Cathalijn Leenaars	
3.	Other contributors (names, affiliations, contributions)		
4.	Contact person + e-mail address	c.h.c.leenaars@uu.nl	
5.	Funding sources/sponsors	ZonMW – MKMD (114024114)	
6.	Conflicts of interest	None	
7.	Date and location of protocol registration	27-12-2017	
8.	Registration number (if applicable)		
9.	Stage of review at time of registration	Searches performed, screening in progress.	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Biomedical research aims to understand human disease on a mechanistic level, in order to develop possible cures. Drug development is a lengthy and expensive process, which relies on pre-clinical experiments (*e.g.* animal experiments) and clinical trials (*i.e.* human experiments). However, candidate drugs that are successful in animal experiments often fail in clinical trials, which leads to a financial burden and even to potentially life-threatening experiences for trial participants. To prevent unnecessary risks and expenses, we need to understand why the outcomes from animal studies fail to translate to humans in phase I-II clinical trials. One perspective is that the concept of animal-to-human predictability is fundamentally mistaken, that it is nothing more than an assumption that was never scientifically tested [1, 2]. Advances in physiology, genetics, epigenetics, molecular biology and other fields support this perspective by demonstrating important differences between animals and humans, which represent a hurdle to translation [3]. The opposite perspective is that biomedical and pharmaceutical research accomplished astonishing breakthroughs during the last decades exactly because of animal experiments as a rule being predictable for humans. Within this perspective, researchers aim to increase translatability by optimizing the	

		design of animal experiments and their reporting [4, 5]. Nevertheless, more reliable outcomes from animal experiments do not necessarily result in improved translation [6]. Moreover, publication bias (i.e. the relative underreporting of negative results) prevents the assessment of true translational failure rates, which can result in unwarranted clinical trials [5]. Both perspectives are currently defended, but in most instances without reference to actual data on animal-to-human predictability. The empirical data to analyse animal-to-human predictability, however, are available in literature, and several authors have started to address animal-to-human translational success rates[7, 8]. Quantitative assessment of the predictability of currently used animal models allows for an ethical discourse of acceptability, and a statistical analysis of predictive value. This systematized review will collect and describe the available quantitative data from studies that assessed animal-to-human translational success rate. We define successful translation as replication in a randomized trial in humans (mainly phase I-II) of statistically significant positive (or negative) results for the primary study outcome as described by the authors in animal experiments. We do not expect to find clinical trial publications after animal experiments with negative results. We prefer to focus on early clinical trials over market access, as successful trials do not always result in clinically available medication for reasons beyond animal-to-human predictability. Besides studies explicitly addressing translational success rates, we will include meta-analyses including both human and animal studies, as they provide quantitative information on translation for individual interventions	
	Research question		
11.	Specify the *condition* of interest	Translation from animal models to humans. We define successful translation as replication in a randomized trial in humans of statistically significant positive (or negative) results for the primary study outcome in animal experiments. Consequently, translational failure is defined as a non-replication of the results of animal experiments in a randomized trial for the primary study outcome.	
12.	Specify the population/species studied	All laboratory animal studies of interventions with human relevance	
13.	Specify the intervention/exposure	Any	
14.	Specify the control population	Clinical trials in humans (preferably phase I and/ or phase II)	
15.	Specify the outcome measures	Quantitative evidence on translational failure or success	
16.	State your research question (based on items 11-15)	What is the observed range of the animal-to-human translational success (and failure) rates within the currently available empirical evidence?	
	C. Methods		
	Search and study identification		
17.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	X MEDLINE via PubMed ☐ Web of Science ☐ SCOPUS X EMBASE ☐ Other, namely: ☐ Specific journal(s), namely:	
18.	Define electronic search strategies (*e.g.* use the step by	The search strategy can be found below the protocol table. It consists of 4 elements to be combined with "AND": animal	

	step search guide[15] and animal search filters[20, 21])	models, translation, human clinical trials and publication type.	
19.	Identify other sources for study identification	X Reference lists of included studies ☐ Books ☐ Reference lists of relevant reviews ☐ Conference proceedings, namely: X Contacting authors/ organisations, namely: see below X Other, namely: personal files	
20.	Define search strategy for these other sources Personalized searches by the authors	Contacting authors: All first and last authors from included studies retrieved by the search or by their reference lists will be contacted to ask if they are aware of other studies meeting our inclusion criteria. Other researchers familiar with the topic within SYRCLE's network will be contacted with the same question. Personal files: All authors of this protocol will check their literature for studies complying with the inclusion- and exclusion criteria.	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	Title/ abstract screening, followed by full text screening for abstracts deemed relevant.	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	a) Two independent reviewers per screening phase will identify relevant studies from the search results and subsequently retrieve the PDF to check if the study complies with our inclusion and exclusion criteria. b) Discussion until consensus is reached, decision by a 3rd person if consensus is not easily reached.	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criterium: study or review quantitatively comparing the results of studies including at least 2 species with one being human. Exclusion criterium: study or review of studies comparing 2 non-human species, or comparing outcomes between human clinical trials.	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: any (laboratory) animal species and humans Exclusion criteria:	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: Any Exclusion criteria:	
26.	Outcome measures	Inclusion criteria: Any type of quantitative information on translation from animal experiments to human clinical trials Exclusion criteria:	
27.	Language restrictions	Inclusion criteria: Any Exclusion criteria: -	
28.	Publication date restrictions	Inclusion criteria: Any Exclusion criteria: -	
29.	Other	Inclusion criteria: systematic or other review, editorial or letter Exclusion criteria: primary study or combination of 2 primary studies	
30.	Sort and prioritize your exclusion	Selection phase: title abstract and full text screening	

	criteria per selection phase	1. Less than 2 species or no human 2. No quantitative information on translation 3. Primary studies	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	-Authors - Year - Title - Journal - Volume, pages - Language - Research department	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	- Type of analysis comparing animal and human data - Numbers of studies, animals and humans included	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	-Type of animal model(s) -Type of clinical trial(s) -Field(s) of research For both animals and humans: -age -sex -disease status	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	-type of intervention -dose -route of administration	
35.	Outcome measures	Any type of quantitative information on translation from animal experiments to human clinical trials	
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	(a) 1 reviewer; a random sample of 5% of the included studies will be checked by a second reviewer. (b) Discussion between reviewers	
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] ☐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: XOther criteria, namely: - Power calculation for the translational comparison, sampling method of the studies included in the analysis, type of data analysis, blinding in the sampling procedure, blinding of the data analyst, control for publication bias. - Compliance with PRISMA guidelines for reviews	
	Collection of outcome data		
39.	For each outcome measure, define the type of data to be	Quantitative data on translation will be described as provided by the authors	

	extracted (*e.g.* continuous/dichotomous, unit of measurement)		
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	- Data extraction from tables and text - If no numerical data are available in tables and/or text we will contact the authors - If no answers are received, digital image software (e.g. a graphic ruler) will be used to obtain values for graphically available data.	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	a) 1 reviewer; a random sample of 5% of the included studies will be checked by a second reviewer. b) Discussion between reviewers	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	Results will be tabulated and qualitatively described.	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	Considering the anticipated variability in the study designs, we will not perform a meta-analysis.	
Final approval by (names, affiliations):		Cathalijn H.C Leenaars, Julia L.M Menon	Date:

PubMed search:

Animal models:
(animal experimentation[MeSH] OR models, animal[MeSH] OR Animals[MeSH] OR animal experiment* [ti] OR animal model* [ti] or animal stud*[ti] OR animal research[ti])

Translation:
(translational medical research[MeSH] OR translat*[ti] OR extrapol* [ti] OR valid*[ti] OR compar*[ti] OR predicta*[ti] OR predicti*[ti] OR predictor*[ti])

Human clinical trials:
(human experimentation[MeSH] OR human*[ti] OR clinical trial*[ti] OR clinical pract*[ti] OR clinic[ti] OR clinical use[ti])

Publication type:
(review[pt] OR letter[pt] OR editorial[pt] OR systematic review [pt])

Embase Search:

Animal models:
exp animal experiment/ OR exp animal model/ OR animal/ OR (animal experiment* OR animal model* OR animal stud* OR animal research).ti,kw.

Translation:
exp translational research/ OR translat*.ti,kw. OR extrapol*.ti,kw. OR valid*.ti,kw. OR compar*.ti,kw. OR (predicta* OR predicti* OR predictor*).ti,kw.

Human clinical trials:
exp human experiment/ OR human*.ti,kw. OR (clinical trial* OR clinical pract* OR clinic OR clinical use*).ti,kw.

Publication type:
review.pt. OR letter.pt. OR editorial.pt. OR short survey.pt.

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5. August, M.I.M.ć.-K.R.S.P. and Schubiger, *Can animal data predict human outcome? Problems and pitfalls of translational animal research.* Eur J Nucl Med Mol Imaging, 2012. **39**: p. 1492-1496.
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