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Exploring the Potential of Simulation Models as Alternatives to Animal Models in Drug Testing and Biomedical Research: A Systematic Review

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ADMINISTRATIVE INFORMATION

Support - Not Applicable.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2024110028

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 November 2024 and was last updated on 7 November 2024.

INTRODUCTION

Review question / Objective How effective are simulation models in replicating the biological processes required for drug testing and biomedical research, and can they serve as viable alternatives to animal models in terms of accuracy, reliability, and ethical considerations.

Rationale Animal models have long been central to drug testing and biomedical research, providing key insights into safety, efficacy, and biological mechanisms. However, ethical concerns, high costs, limited scalability, and the poor translation of animal findings to human outcomes have driven the search for alternatives. Simulation models, including computational and in silico approaches, offer a promising alternative by accurately mimicking human biological processes. These models can reduce the reliance on animal testing while offering more relevant and efficient methods for predicting human drug responses and disease dynamics.

This systematic review focuses on the potential of simulation models to address critical challenges in drug development and biomedical research. By evaluating their effectiveness in replacing animal models, particularly for drug safety and efficacy testing, the review supports the growing demand for humane, ethical, and accurate methods that better reflect human biology. These alternatives hold significant potential for improving patient outcomes and streamlining drug development while minimizing the ethical issues associated with animal experimentation.

Condition being studied The focus of this systematic review is on human diseases and conditions commonly modeled for drug testing and biomedical research, particularly those with high unmet medical needs, such as cancer, cardiovascular diseases, neurodegenerative disorders, diabetes, and infectious diseases. These diseases often involve complex physiological processes, making it challenging to accurately predict drug responses in humans using animal models alone. Simulation models, including in

silico and computational methods, offer promising alternatives by replicating human biology and disease mechanisms more precisely. By utilizing patient-specific data, genetic information, and physiological parameters, these models aim to improve the accuracy of drug efficacy and safety predictions, reducing the reliance on animal models and enhancing personalized medicine approaches. The review will explore how simulation models are being developed and applied in these domains to better predict health outcomes and optimize therapeutic interventions.

METHODS

Search strategy PubMed (MEDLINE), Embase, Scopus, ScienceDirect.

Participant or population Inclusion Criteria:
Species: Studies involving commonly used animal models, including rodents (e.g., mice, rats), rabbits, non-human primates, pigs, and other mammals typically employed in preclinical drug testing.

Sex: Both male and female animals will be included to account for sex-specific differences in drug response and disease progression.

Disease Models: Studies utilizing animal models of human diseases for drug testing, including but not limited to cancer, diabetes, cardiovascular diseases, neurological disorders, and infectious diseases. Models simulating pharmacokinetics, pharmacodynamics, and toxicological assessments will also be included.

Experimental Interventions: Studies that compare traditional animal-based models with in silico or simulation models for drug efficacy, safety, toxicity, or other biomedical applications.

Intervention This systematic review will examine the use of simulation models as alternatives to animal models in drug testing and biomedical research. The interventions of interest will include computational simulations, in silico models, and other advanced simulation technologies designed to replicate biological processes or disease states that are traditionally modeled in animals.

Inclusion Criteria:
- Types of Models: Computational simulations (e.g., systems biology models, pharmacokinetic/pharmacodynamic (PK/PD) models, molecular simulations, agent-based models)
In silico models (e.g., virtual organs, tissue models, multi-scale simulations)
Predictive algorithms that simulate drug responses, toxicology, or disease progression

- Applications: Drug testing (e.g., efficacy, safety, toxicity studies)
Disease modeling (e.g., models simulating Type 1 diabetes, cancer, neurodegenerative diseases)
Biomedical research applications (e.g., organ function simulations, human tissue simulations, virtual clinical trials)

- Usage Scenarios: Simulations designed to replace or reduce animal use in preclinical drug discovery, safety evaluations, and toxicology studies.
Simulation models developed for pharmacokinetics, pharmacodynamics, and ADME (absorption, distribution, metabolism, and excretion) studies.
Models replicating specific animal procedures or disease models, such as simulating a high-fat diet to mimic metabolic disorders or virtual organ models used to assess organ toxicity.

- Simulation Parameters: Detailed descriptions of the model's parameters, including dosage, timing, and frequency of simulated drug administration or exposure.
Studies describing the methodology, validation, and accuracy of these simulation models compared to traditional animal models.

Comparator In this systematic review, the comparator or control interventions will include traditional animal models used in drug testing and biomedical research, as well as any other relevant in vivo models and will be compared with the simulation model. Specifically, eligible control groups will consist of:

Vehicle-treated animals, where animals receive a placebo or non-active substance.
Sham-treated animals, where animals undergo a procedure that mimics the experimental intervention but without the active component.
No treatment control, where animals receive no intervention and serve as a baseline for comparison.
Baseline measurements, where pre-experiment data from the same animals or cohorts are used as a control group.

Inclusion criteria for control interventions:
Studies that utilize one or more of the above-mentioned control groups in drug testing or biomedical research.

Studies that use control groups for comparison with simulation models, computational approaches, or in vitro methods.
Studies that include detailed descriptions of the control conditions and methodologies used to ensure appropriate comparison with simulation models.

Study designs to be included - Studies that assess the efficacy of simulation models in replicating outcomes typically derived from animal models.- Studies that directly compares simulation models to animal models in drug testing, toxicity assessment, or other biomedical research areas.

Eligibility criteria This systematic review will examine the use of simulation models as alternatives to animal models in drug testing and biomedical research. The interventions of interest will include computational simulations, in silico models, and other advanced simulation technologies designed to replicate biological processes or disease states that are traditionally modeled in animals.

Inclusion Criteria:
- Types of Models: Computational simulations (e.g., systems biology models, pharmacokinetic/pharmacodynamic (PK/PD) models, molecular simulations, agent-based models)
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Main outcome(s) Outcome Measure(s)
The primary outcome measures to be considered for inclusion in this systematic review will focus on the effectiveness and validity of simulation models as alternatives to animal models in drug testing and biomedical research. Specific outcome measures will include:

- Predictive accuracy: The ability of simulation models to accurately predict drug efficacy, toxicity, pharmacokinetics, and pharmacodynamics, as compared to traditional animal models.

- Translational relevance: The extent to which the results from simulation models can be extrapolated to human physiology and disease conditions.

- Reduction in animal usage: Quantitative measures of how the implementation of simulation models has reduced the need for animal models in drug development and biomedical research.

- Cost-effectiveness: A comparison of the financial costs of using simulation models versus animal models for drug testing and biomedical research.

- Regulatory acceptance: Assessment of whether simulation models are accepted or endorsed by regulatory agencies (e.g., FDA, EMA) as replacements for animal models in drug testing protocols.

- Technological feasibility and implementation: The ease with which simulation models can be implemented in research settings, including the availability of necessary software, hardware, and expertise.

- Ethical impact: Evaluation of the ethical implications of adopting simulation models over animal models, focusing on the reduction of animal suffering and alignment with the 3Rs principles (Replacement, Reduction, and Refinement).

Quality assessment / Risk of bias analysis To assess the risk of bias and overall quality of studies in this systematic review, we will use SYRCLE's risk of bias tool and the CAMARADES checklist.

SYRCLE's Risk of Bias Tool will evaluate potential biases in animal studies and be adapted for simulation studies comparing with animal models. It covers key domains such as sequence generation, allocation concealment, blinding, and outcome reporting.

The CAMARADES Checklist will complement this by assessing study quality, focusing on elements like randomization, blinding, sample size calculations, and conflicts of interest. For simulations, emphasis will be placed on model transparency, validation, and comparison with animal models.

Two independent reviewers will apply these tools, with any discrepancies resolved by discussion or consultation with a third reviewer. The results will be summarized in a table, highlighting bias domains, quality ratings, and key concerns.

Strategy of data synthesis Given the expected heterogeneity of studies exploring the potential of simulation models as alternatives to animal models in drug testing and biomedical research, it is expected that a narrative synthesis will occur. First, study characteristics will be summarized, including study designs, types of simulation models used, and their intended applications, such as drug testing or disease modeling. The comparative performance of simulation models in relation to traditional animal models or other in vitro methods will be analyzed, with attention to strengths and limitations reported by the studies. Key outcome measures, such as predictive accuracy, validation methods, replicability, and generalizability, will be evaluated. Additionally, the scope and applications of simulation models across various biomedical fields will be mapped, identifying areas where these models are most effective or still underdeveloped. Finally, common challenges and barriers, including computational limitations, lack of standardization, and difficulties in model validation, will be identified, along with potential strategies to address these issues.
Text and tables will be used to provide a descriptive summary and explanation of study characteristics and findings.

Subgroup analysis Not applicable.

Sensitivity analysis Not applicable.

Country(ies) involved USA.

Keywords Simulation models; Animal alternatives; Drug testing; Biomedical research; In silico models; Computational simulations; Non-animal testing; Toxicology; Pharmacokinetics; Drug efficacy; Mechanistic.

Dissemination plans A paper will be submitted to a leading journal in this field.

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