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Review Article

In Silico Clinical Trials in Drug Development: a Systematic Review

Bohua Chen

Faculty, University Medical Center, Göttingen, Germany

I N F O

E-mail Id:
bohua.chen@med.uni-goettingen.de

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A B S T R A C T

In the context of clinical research, computational models have received increasing attention over the past decades. In this systematic review, we aimed to provide an overview of the role of so-called in silico clinical trials (ISCTs) in medical applications. Exemplary for the broad field of clinical medicine, we focused on in silico (IS) methods applied in drug development, sometimes also referred to as model informed drug development (MIDD). We searched PubMed and ClinicalTrials.gov for published articles and registered clinical trials related to ISCTs. We identified 202 articles and 48 trials, and of these, 76 articles and 19 trials were directly linked to drug development. We extracted information from all 202 articles and 48 clinical trials and conducted a more detailed review of the methods used in the 76 articles that are connected to drug development. Regarding application, most articles and trials focused on cancer and imaging related research while rare and pediatric diseases were only addressed in 18 and 4 studies, respectively. While some models were informed combining mechanistic knowledge with clinical or preclinical (in-vivo or in-vitro) data, the majority of models were fully data-driven, illustrating that clinical data is a crucial part in the process of generating synthetic data in ISCTs. Regarding reproducibility, a more detailed analysis revealed that only 24% (18 out of 76) of the articles provided an open-source implementation of the applied models, and in only 20% of the articles the generated synthetic data were publicly available. Despite the widely raised interest, we also found that it is still uncommon for ISCTs to be part of a registered clinical trial and their application is restricted to specific diseases leaving potential benefits of ISCTs not fully exploited.
Key words: In silico, systematic review, clinical trial, pediatric disease, rare disease, Model Informed Drug Development.

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Introduction

The development of new drugs is both costly and time-consuming.[1] Among other measures, the implementation of sophisticated and appropriate quantitative methodology in the development process may enhance the efficient use of resources. Computational models have evolved from a mere alternative data source (e.g. to clinical trials) to providing a toolbox for the efficient development of new medicines, for drug maintenance on the market, and the extension of indications for existing drugs (i.e. their re-purposing in completely new indications).[2]

In silico clinical trials (ISCTs) prove particularly useful in studies in contexts where researchers struggle to enrol sufficient numbers of participants, like studies addressing rare or pediatric diseases. The generated synthetic data may augment data from clinical studies, thus enhancing the evidence base. The availability and appropriate use of methods to synthesize different types of evidence then becomes key to an impartial and accurate assessment of the overall evidence.[3] In particular, different types of evidence, as derived from randomized experiments, real world data, or computational models needs to be treated with appropriate consideration of their exact relationships and potential biases to allow for robust and reliable conclusions.[4] Regulatory agencies such as U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) have already considered issues in extrapolation methods for pediatric populations by issuing dedicated guidelines.[6, 7]

A variety of model-based approaches and applications have recently been defined as ModelInformed Drug Development (MIDD) by regulatory agencies and industry.[5] In particular, ISCTs can be used to supplement or substitute real patients with model-based simulations as part of MIDD. MIDD, as defined in the ICH-MIDD roadmap[5] and considered in the present review, involves more than just pharmacokinetic/ pharmacodynamic (PK/PD) models.

The present article aims to review the impact of computational models in clinical medicine over the past decades, with a particular focus on drug development. To this end, we performed a systematic review aiming at journal publications describing or applying in silico (IS) methodology, and at registered clinical trials related to ISCTs. We sought to provide a comprehensive overview of the recent development of ISCTs, while also exploring differences in definitions used by various institutions. We outline the application of ISCTs across various diseases, especially rare and pediatric diseases, and provide detailed examples of the use of computational models in these specific contexts. In addition, we also consider methodological aspects, including the different types of computational models, the data sources used to inform them, and the reproducibility of published results.

The remainder of this article is structured as follows. In the following "Methods" section, the terminology and methods used in the systematic review are described, while the characteristics of the publications and trials identified are summarized in Section "Results", including a closer look at three exemplary cases from the review and how IS methods were utilized. Finally, the paper closes with a discussion.

Methods

Terminology

The exact definition of an ISCT varies between fields of application and between regulatory agencies. For example, the International Organization for Standardization (ISO) characterized an ISCT by "[...] the use of individualized computer simulation in the development or regulatory evaluation of a medicinal product, medical device or medical intervention"[8] A similar, more detailed definition was given by the U.S. Food and Drug Administration (FDA);[9] they defined an ISCT as "[...] an emerging application of computer modelling and simulation (CM&S) where device safety and/or effectiveness is evaluated using a 'virtual cohort' of simulated patients with anatomical and physiological variability representing the indicated patient population". The purpose of ISCTs is described to include "[...] augmenting or reducing the size of a real world clinical trial, providing improved inclusion-exclusion criteria, or investigating a device safety concern for which a real world clinical trial would be unethical"[9] Most recently, in the white paper by Musuamba et al.,[2] ISCTs are defined as a "class of trials for pharmacological therapies or medical devices based on modelling and simulation technologies". Furthermore, it is stated that the ISCTs' purpose is to "[...] produce digital evidence that can serve in complement to or replacement of in vivo clinical trials for the development and regulatory evaluation of medical therapies".[10]

The common element in all of these definitions is the use of computer modelling and simulations to evaluate a diagnostic device or therapy. In contrast to the ISO, who kept their definition quite broad, Musuamba et al. and the FDA specifically characterized the purpose of an ISCT as to complement evidence from clinical trials. In the following, we adhere to the brief and concise definition of ISCTs given by Musuamba in 2021[2] Moreover, we clearly distinguish between data analysis, which plays a distinct role in modern clinical medicine, and 6 data generation, which typically involves simulating biological systems and patients' outcomes rather than observing them experimentally.

The set of rules or the algorithm describing the behaviour of the biological system is called an IS model if it is implemented and studied computationally[2] IS models play a crucial role in generating digital evidence and since we later focus on drug development as one exemplary

application field of ISCTs, we briefly outline some of the terminology and models frequently used in the field of model-informed drug development. The term IS model refers to a broader class of computational models ranging from fully mechanistic to fully data-driven models and encompasses deterministic models as well as stochastic models. Mechanistic models are typically deterministic and defined by a set of theoretical rules and algorithms based on known or hypothesized mechanisms, while data-driven models are developed from observations or data with the aim of inferring a set of rules explaining those data.[2] For example, pharmacokinetic (PK), pharmacodynamic (PD) and PK/PD models may describe the doseconcentration, the concentration-response and the dose-response relationship of a given drug through ordinary differential equations and rely to a varying degree on data to estimate parameters or even solely use those known from literature. A more comprehensive study of PK, PD and PK/PD models can be found in[11,12] Extensions of the classic PK model, called physiologically-based pharmacokinetics (PBPK) and physiologically-based biopharmaceutics modelling (PBBM), are extensively explained in[13,14] respectively. A crucial aspect of successful model development is a solid understanding the underlying disease. Disease progression models describe how the disease dynamics are modified under the drug intake and can therefore be used to complement a PK/PD model. A good description of disease progression models and their use is provided in.[15] Quantitative systems pharmacology (QSP) is broadly defined as an approach to translational medicine that integrates PK, PD and disease progression modelling and aims at elucidating and validating new pharmacological concepts as well as applying them to the drug development process.[2] A review of QSP modelling cases can be found in[16] To move from a patient-centred perspective to a population based approach and allow some variability in the effect of a drug, the corresponding PK and PD parameters may be modelled as random variables. This class of models is called population-based PK (popPK) or population-based PK/PD (popPK/PD), depending on which relationship is considered, and always requires patient data in addition to the mechanistic knowledge behind the PK and PD mechanisms to infer the underlying probability distribution. A more detailed explanation is given by[17] Models based on artificial intelligence, e.g., machine learning or deep learning, heavily depend on the training data and do not necessarily reflect the actual underlying mechanisms accurately so that extra caution is necessary when extrapolating beyond the training data[2]. It is important to note that there is no generally accepted framework on how to differentiate all these models and their scope of application clearly and without overlap. An overview over some of the above mentioned model terms can be found in[2,9]

Systematic literature search and trial selection

We restricted our search to one literature database and one clinical trials registry. For both we chose the most popular ones (i.e. PubMed and clinicaltrials.gov, respectively), in order to review the methodology of ISCTs and their impact on clinical medicine.

Starting with PubMed, we searched for the phrases “in silico clinical trial” or “virtual clinical trial” in articles published up to December 31, 2023. During the initial screening process of the resulting abstracts, we evaluated the relevance of the retrieved papers to our systematic review using the definition of ISCTs by[2] At least two reviewers independently reviewed the abstracts and any disagreement was resolved by a third reviewer. We specifically excluded papers where computers were only used for image processing, endpoint evaluation, or treatment decision support, as these do not aim to reduce patient exposure to medical devices or therapies. The term “virtual trial” was sometimes used to refer to study designs where patients participate remotely, so papers referring to that meaning of the term “virtual” were also excluded. We further restricted our analysis to articles with a strong connection to ISCTs, eliminating articles that prepare for future ISCTs or simply validate the results of ISCTs. In a second step, we classified the remaining papers into three categories: “review”, “application” and “methods” in order to understand the field of research better. A “review” article gives a comprehensive summary of a broad or specific topic, an “application” article reports the protocol or results of actual ISCTs, and a “methods” article focuses on the IS model itself. The full list of included articles is provided in the supplementary material online, in Table S1.

As we are particularly interested in drug development and the methodology used in this application field of ISCTs we screened the remaining articles regarding their connection to drug development. We analysed the methodological aspects like the used model and the reproducibility of results by considering only articles with a clear connection to a specific drug compound. This included the development of novel drugs as well as trials related to dose finding, drug re-purposing and new combinations of existing drugs. Papers without a link to these topics or those that did not mention a specific drug compound are excluded. Typical examples of excluded articles are related to imaging techniques and surgical methods as well as to the development of models that can be used for drug development in the future without naming any specific drug.

We searched the ClinicalTrials.gov database for registered clinical trials beginning before December 31, 2023 using the search phrase “in silico”. At least two authors independently reviewed the study description and a third reviewer was consulted in cases of disagreement. In general, we included

trials that applied IS methodology in all areas of medicine, regardless of study design or study population. Trials that do not perform an ISCT itself, but aim to lay the groundwork for future simulations by collecting data to inform IS models or evaluate results from previous ISCTs fall into the category "Preparation for future ISCTs" and "Validation of ISCT results", respectively. Trials in one of these categories are not excluded but considered relevant for further analysis and therefore the inclusion and exclusion criteria regarding the relevance of trials differ from those applied to the PubMed articles. Trials that incorporate an ISCT at some point in their process are classified as "application". The categories "methods" and "review" were not applied in the context of clinical trials. The full list of included clinical trials is provided in the supplementary material online, in Table S1.

Data extraction and analysis

Analysis of journal articles

We extracted general and application-related information for all journal articles classified as relevant no matter their relation to the field of drug development and considered only articles with a direct connection to drug development, i.e., articles that target a specific drug compound, for methodology-related information.

Country and publication year

We used the publication date to investigate the interest in ISCTs over the past 30 years and the country of the first author's affiliation to analyse geographical aspects. To take into account the increase in the number of publications in general, we calculated the proportion of IS related articles among all articles with the keyword "clinical trials" for the corresponding year

Disease classification

To determine which diseases IS modelling was applied to, we used the International Classification of Diseases, 11th Revision (ICD-11), which is divided into 26 chapters, each representing a distinct disease category. Most chapter names are self-explanatory, e.g., chapter 2 "Neoplasms" contains all diseases characterized by uncontrolled and abnormal growth of cells. Chapters that need further clarification are "Factors influencing health status or contact with health services" and "Extension codes". The first one describes screenings and preventive examinations like CT scans and X-rays e.g. mammographies, the latter provides additional context to diagnoses, such as indicating that a condition is related to a medication, e.g. adverse reactions. We also added the category "General diseases" in the case the article did not mention a specified disease e.g. the article only describes the modelling of the immune system in general and not in response to a specific infection.

Rare or pediatric disease context

As ISCTs can be used to reduce the number of trial participants, they promise to be particularly useful in the contexts of rare and pediatric diseases. In this review we refer to a disease as rare, if it affects less than 1 in 2000 people, which is the European Commission's definition[18], or when it has an entry in the Orpha.net database. We refer to a disease as pediatric, when it is only or mostly prevalent in people younger than 18 years.

Relation to drug development

In the next step, we wanted to gain a deeper understanding of which particular IS modelling approaches were used in the field of drug development. We categorized the models as reported by the authors if the model class was specifically stated. In cases where the model was only referred to as mathematical or computational, we classified it according to the terminology section, if possible. The resulting 8 categories are: PKPD, PBPK, PBBM, disease progression, QSP, popPK, artificial intelligence based approaches, and other models. The latter category contained all the articles that could not be classified by us due to missing information on the model.

Conclusion

- **Advancements in ISCTs:** The review acknowledges the substantial progress made in developing computational models that simulate human physiology, enabling more accurate predictions of drug efficacy and safety.
- **Challenges to Implementation:** Despite advancements, the authors note that the integration of ISCTs into the drug development pipeline is limited. Barriers include a lack of standardized methodologies, insufficient regulatory frameworks, and limited availability of high-quality data for model validation.
- **Recommendations for Future Research:** The authors advocate for increased collaboration among stakeholders, including researchers, regulatory agencies, and industry partners, to establish standardized protocols and regulatory guidelines. They also emphasize the need for open-access data sharing to enhance model accuracy and reproducibility.
- **Potential Impact:** With the resolution of existing challenges, ISCTs have the potential to significantly streamline the drug development process, reduce reliance on animal testing, and facilitate the development of personalized medicine approaches.

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