In silico clinical trials for paediatric orphan diseases



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Abstract

In silico clinical trials provide an effective solution to the obstacles encountered in carrying out *in vivo* clinical trials. They have the potential to transform the approach of investigating and developing treatments for rare conditions, thereby enhancing the quality of life for individuals worldwide. To enhance existing treatment approaches, the utilization of mechanistic and data-driven modelling proves to be beneficial. These tools allow for the simulation and analysis of data obtained from *in vivo* clinical trials, as well as the categorization of subject populations. This technique has the capacity to completely transform the future of drug discovery, particularly for rare paediatric diseases.

1. Introduction

In medical research, the term "*in silico*" refers to conducting experiments on a software via computer simulation. This innovative approach is rapidly gaining attraction in the field of drug development, and it is also being explored for paediatric orphan diseases. Orphan diseases are conditions with low prevalence, the World Health Organisation (WHO) defines this as fewer than 6.5 to 10 patients per 10,000 (1). Approximately >7000 uncommon illnesses impact 25 to 30 million individuals, with roughly 4000 orphan diseases, and around 5000 patients for each orphan disease require medical attention in the United States (2). Rare disease prevalence is estimated to range from 5 to 76 per 100,000 people in non-North American and European countries. This conservative estimate puts the total number of affected individuals worldwide to about 446.2 million. There are currently 230 rare diseases being researched in the Rare Diseases Clinical Research Network (RDCRN) (3). Approximately 80% of these uncommon illnesses have a known genetic cause that involves one/more genes or chromosomal abnormalities. The rest are due to degenerative, proliferative, or teratogenic causes, allergies, or infections (bacterial or viral) (4). There were just 34 therapies available for uncommon illnesses before 1983 (2,3). As of 2021, more than 600 therapies had been approved as a result of government incentives over the previous 40 years. Despite the progress recorded, only a small percentage of patients can be treated with an approved medications. As such, between 2010 and 2015, one-third of all new drug approvals for rare diseases were granted (3). Traditional clinical trials for these diseases face significant challenges, including limited patient populations, ethical concerns, and high costs. *In silico* clinical trials offer a promising solution to these challenges, revolutionizing the way we study and develop treatments for paediatric orphan diseases.

2. Understanding the challenges

Paediatric orphan diseases present unique challenges that hinder traditional clinical trial methods. Even though public awareness has increased over the past three decades, research on rare diseases faces obstacles that include scarcity of qualified disease experts, the difficulty of securing funding for research due to limited economic impact, patient distribution across geographic regions that hinder patient recruitment for clinical trials, the requirement for specialised study designs to address the small patient cohorts, and high patient variability throughout the course of rare diseases. The rarity of these diseases makes it difficult to recruit a sufficient number of patients for meaningful clinical trials. Furthermore, because children account for 50% of patients with rare diseases, so because of ethical concerns clinical research becomes more difficult (1). It is challenging to conduct conventional randomized clinical trials (RCTs) in parallel groups due to the small patient numbers dispersed over a large geographic area. Both the inclusion of particular populations and therapies that are customized for each patient are necessary. Unfortunately, there is little to no evidence supporting the clinical trial results that are most frequently published for rare diseases. It is inappropriate to use "before/after" methodology studies without a control group or historical comparisons when evaluating drugs because these studies could be potentially biased (4). Moreover, the high costs associated with traditional trials make it financially challenging for pharmaceutical companies to invest in developing treatments for these diseases.

3. The role of *in silico* virtual clinical trials

To overcome the problems associated with a small population available for conventional clinical trials, the use of *in silico* computational models and simulations is proposed. The essential elements and biological mechanisms are first expressed in a conceptual model for *in silico* clinical trials, after which they are converted into a mathematical format (1). The limitation of small patient cohorts in rare diseases can be overcome by creating hundreds of different parameter sets *in silico*, allowing for the establishment of a large cohort of virtual subjects. Additionally, the *in silico* model is used to create a distinct paired data set of both treated and untreated virtual subjects, avoiding the difficulties that come with paediatric RCTs (4). These trials can simulate the biological processes of a disease, the effects of a drug on the body, and the likelihood of success in a virtual population (Figure 1). By leveraging data from various sources, including genomics, proteomics, and clinical studies, researchers can create sophisticated models that accurately represent the complexities of paediatric orphan diseases.

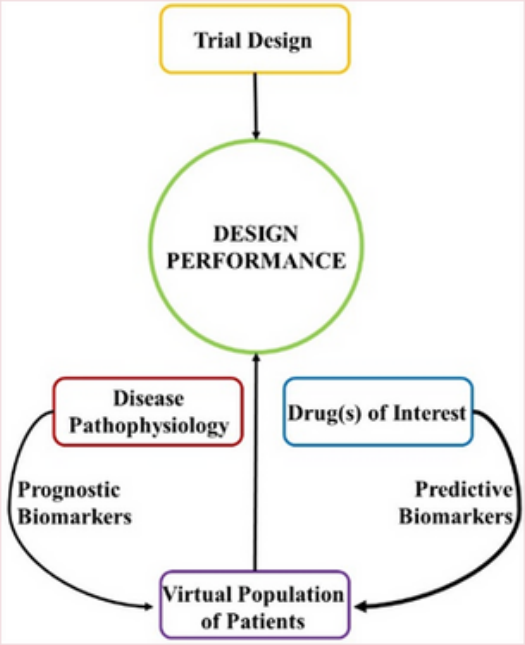

Figure 1. Essential components for modelling and simulation approach

3.1 Collection of databases

The first step to prepare any computational clinical trial model is to gather comprehensive information about a particular disease from already established clinical databases. Patient registries from a geographically defined population over an extended period, provide the highest level of evidence for epidemiological studies. These databases aim to provide data on every facet of a specific rare disease, organized into multiple primary categories (Table 1) (4). The FDA database includes 1055 medications list and provides information on the indications related to orphan drug and chemical structures (3).

Table 1. Data sources for rare diseases (3)

Dataset	Use	Reference
FDA Orphan Drug Designations and Approvals	Drugs associated with rare diseases	www.accessdata.fda.gov/scripts/opdlisting/oopd/
MalaCards	The human disease database	www.malacards.org/
Pharos	Targets associated with diseases	https://pharos.nih.gov/
ClinVar	Gene variations and associated conditions	www.ncbi.nlm.nih.gov/clinvar/
OMIM	Association between human genes and genetic disorders	https://omim.org/
GeneCards	Genes information	www.genecards.org
NORD	Signs and symptoms of rare diseases	https://rarediseases.org/
Rare Disease InfoHub	Symptoms of rare diseases (including experts and funding opportunities)	https://rarediseases.oscar.ncsu.edu/
Genetic and Rare Diseases Information Center	Synonyms, summary, and symptoms for rare diseases	https://rarediseases.info. nih.gov/

3.2 Analysis of databases

3.2.1 Prognostic biomarkers

A biomarker is considered prognostic when its values at the beginning or its changes over time are linked to a clinical outcome that is unrelated to the treatment. Prognostic biomarkers are linked with a specific favourable or unfavourable evolution of the disease. Its correlation with the clinical endpoint needs to be consistently shown in separate investigations, ideally spanning a variety of clinical scenarios, for it to be considered validated. Contrary to popular opinion, heterogeneity is typically more advantageous from a statistical standpoint than disadvantageous. Prognostic biomarkers may only need to be initially identified and statistically validated through retrospective studies; however, prospective studies may be required to confirm the clinical utility of the biomarker (4).

3.2.2 Predictive biomarkers

A biomarker is considered predictive when it is shown that its initial value or subsequent changes can accurately predict the effectiveness or harmful effects of a treatment, as judged by a certain clinical outcome. RCT data involving patients with high and low biomarker levels is necessary for the statistical identification of predictive markers. To find potential predictive biomarkers and validate them sufficiently for inclusion in clinical practice and trial designs, retrospective analyses might be adequate. However, for conclusive evidence, prospective clinical trials might still be required (4).

3.2.3 Analysis of potential treatments

Various methodologies have been proposed to assess the impacts of interventions in observational studies. The primary goal of all these techniques is to address confounding, or potential bias brought on by the nonrandomized treatment assignment (5). The most popular techniques are:

i. Observational study designs: Case-crossover, Case time-control, Historical controls, Treatment candidates, Comparisons of treatments for the same indication
ii. Data-analytical techniques: Asymmetric stratification, Propensity score adjustment, Two-stage least squares, Common multivariable statistical techniques, Instrumental variables, Simultaneous equations, Stratification and matching on specific covariates

3.3 Disease/drug effect modelling

Several models of diseases have been published in the literature thus far. Their mathematical formulation relies on partial differential equations (PDEs) and/or ordinary differential equations (ODEs), which serve as the foundation for these models. These models are often used to simulate the progression of biomarkers during the course of disease development. Pharmacokinetic-pharmacodynamic relationships serve as the foundation for treatment effect modelling most of the time, and models on this subject are already available. These models are particularly helpful in anticipating biomarker changes following a modification in the dosage of a treatment (5).

4. Strategy for simulation

Conducting simulated clinical trials of a drug in virtual populations allows for direct observation of the treatment's effect impact on the diseased population. Any simulation model for a given therapeutic technique is categorized into one of these sub-models (6):

- Patient outcomes are predicted by the input-output (IO) sub-model. It includes the pharmacokinetic/pharmacaodynamic (PK/PD) characteristics of the medicine, as well as a pathophysiology model of the condition, if exists. In order to accurately replicate drug concentrations, biomarkers of therapeutic or toxicological response, or the occurrence of a clinical outcome or adverse event, it is necessary to determine the parameters and structure of the model using the data obtained from clinical research.

- Using already-existing patient databases, the covariate distribution sub-model explains patient features.

- The execution sub-model describes the features of experimental designs and deviations from protocol that are related to patients or researchers.

Assessment of simulation results: Assessment is carried out in the same population following drug or placebo exposure. This method allows for the exploration of a wide range of scenarios pertaining to RCT designs, drug dosages, drug associations, patient selection, exposure duration, etc. The following are the primary steps:

1. Patient samples for in silico RCTs that are chosen at random from the "validated" virtual population.
2. Optimizing and limiting the number of simulations by using a pre-established simulation strategy.
3. Applying the same particular statistical analysis to every set of simulated RCT outcomes.

Analysis of simulation results: The final analysis should identify the most relevant medications (using multiple-criteria decision analysis techniques) and experimental designs for phase III RCT evaluation.
The majority of this analysis would be descriptive. The number of times a significant result is produced in each trial should be used to rank each scenario, including trial design and "rare disease-drug" pairs. Trial length and the accuracy of treatment effect estimates are considered in this final hierarchy (6).

5. Case study (1)

Mutations in Neurofibromatosis Type 1 (NF1) are linked to congenital pseudoarthrosis of the tibia (CPT). A gradual bending of the tibia that leads to spontaneous fractures in the distal portion of the tibia is the hallmark of the unusual condition known as CPT. Pseudoarthrosis is usually caused by insufficient bone regeneration and is treated with either internal or external fixation or by physically excising the abnormal bone tissue. Recombinant human bone morphogenetic protein, or rhBMP-2 or rhBMP-7, is used in clinical practice these days to improve surgical outcome. Nonetheless, there is ongoing controversy regarding the efficacy of BMP therapies, and the United States Food and Drug Administration (U.S. FDA) has cautioned against using BMP in patients who are skeletally immature. Researchers concentrated on the eight parameters that were identified in the literature as having a part in the inadequate fracture-healing outcome in CPT. In order to investigate the impact of the NF1 mutation on bone-fracture repair, the parameter values of the variables representing the abnormal cellular activity of NF1-haplodeficient and NF1-null cells were varied throughout a wide range in the computational model.

Following is the list of selected eight parameters (normal and NFI range respectively):

- Invasion time fibroblasts (3, 0-50)
- Fibroblastic proliferation (0.1, 0.1-10)
- Fibroblastic differentiation (0.01, 0.01-1)
- Osteogenic differentiation (20, 0-20)
- Endochondral ossification (1000, 0-1000)
- Cartilage formation (0.2, 0-0.2)
- Fibrous tissue formation (0.2, 0.2-10)
- Angiogenic growth factor production (10^3, 10^3- 10^5)

Method: The *in silico* clinical trial comprised of 200 virtual individuals, where the healing process was simulated both with and without BMP treatment. The JMP "Design of Experiments" (DOE) tool was used to create the 200 virtual subjects. By primarily modifying the parameter values of the eight components in one direction relative to the normal case, the parameter space was identified, biasing the DOE design toward a CPT phenotype. One generic osteochondrogenic growth factor (gbc) was used to model BMP treatment. This model allows for the simulation of the effects of multiple growth factors that are released from the BMP sponge as a clinical treatment and are present in the fracture callus.

Observation: The complication index (CI) mathematically analyses the degree of severity of CPT by integrating the three most prevalent symptoms a non-union, haematoma, and presence of fibroblasts in a linear form. When a combination of criteria results in decreased CI value, it suggests a low level of CPT severity, implying that the fracture healing process is progressing reasonably smoothly. On the other hand, a combination of criteria that generates a high confidence interval (CI) implies considerably reduced fracture healing and is similar to the CPT phenotype.

Results: Using an arbitrary cut-off of CI value of 0.5, four distinct groups were clustered comprising the virtual subjects:

1. Adverse responders (having a high CI when treated, but a low CI when left untreated)
2. Non-responders, both with and without treatment (high CI)
3. Asymptomatic (low CI, both with and without treatment)
4. Responders (lower CI after treatment and higher CI when left untreated)

In order to identify highly correlated (redundant) attributes, researchers first computed the Spearman correlation matrix of the dataset, the outcomes indicated the lack of association between the NF1 parameters. The correlation between the CI value and the bone tissue fraction was as anticipated to be negative and positive with the fibrous tissue fraction. To conduct a more thorough analysis of the CI data, they examined the various elements that make up the CI value, such as the quantity of fibrous tissue remaining after 49 days. There was a fascinating difference in the amount of fibrous tissue for each subject class at day 49 post-treatment, with the responding subjects having substantially less fibrous tissue than the other subject classes. Every virtual patient was made to experience both no treatment and a treatment with bone morphogenetic protein (BMP). It was demonstrated that, although very subject-specific, BMP treatment significantly reduces the degree of severity of CPT (1).

6. Regulatory requirement for *in silico* models

The regulatory authorities around the world share the need for regulatory guidance for in *silico* model validation. When the modelling and simulation data are merely regarded to have a descriptive role and the crucial information for the question being answered comes from other sources, the regulatory impact is deemed to be minimal. Nonetheless, the regulatory impact is judged to be substantial when modelling results serve as the primary source of evidence to address the important question by substituting data normally generated in a clinical trial (7). Two global regulatory bodies that embrace and promote the use of modelling and simulation in the regulatory process are the European Medicines Agency (EMA) and the U.S. Food and Drug Administration. Further efforts are needed from other regulatory bodies across the globe to integrate this new evidence into the regulatory framework (8).

7. Conclusion

In silico clinical trials hold immense promise for the future of drug development, particularly for paediatric orphan diseases. Today, researchers can successfully conduct an in silico clinical trial, and analyse the outputs. The next logical step would be to compare the simulated cohort with the real patient-specific parameter distributions. As computational models become more sophisticated and data sources become more abundant, the accuracy and reliability of in silico trials will continue to improve. This approach has the potential to revolutionize the way we develop treatments for rare diseases. To improve current treatment strategies, mechanistic and data-driven modelling are helpful tools for simulating and mining data from in silico clinical trials and stratifying subject populations.

This kind of robust modelling can also be used to identify biomarkers, optimize dosage, or determine how long to propose an intervention. Validating in silico clinical trials for rare diseases and identifying any flaws in the computational model in the event of differences between the predicted and measured in vivo outcomes would be made possible by real patients participating in in vivo experiments.

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