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HEADING: DRUG AND ORPHAN DISEASES

A methodological framework for drug development in rare diseases.

The CRESim program: epilogue and perspectives

The CRESim program: methodological framework for drug development in rare diseases

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Summary

Based on the ‘European Child-Rare-Euro-Simulation’ (CRESim) project, this article proposes a generalizable strategy utilizing datasets analysis in combination with modeling and simulation, in order to optimize the clinical drug development applied in the field of rare diseases. The global process includes the simulation of a realistic virtual population of patients (modeled from a real dataset of patients), the modeling of disease pathophysiological components and of pharmacokinetic-pharmacodynamic relations of the drug(s) of interest, the modeling of several randomized controlled clinical trials (RCTs) designs and the analysis of the results (multi-dimensional approach for RCTs durations and precision of the estimation of the treatment effect). However, whereas modeling and numerical simulation may provide supplementary tools for drug development, they cannot be considered as a substitute for RCTs performed in ‘real’ patients.

KEY WORDS

Integrative modelling; Numerical simulation; Randomized controlled clinical trials; Drug development; Rare diseases

Abbreviations

CRESim: Child-Rare-Euro-Simulation

FDA: Food and Drug Administration

IO: input-output (model)

M&S: modeling and simulation

ODE: ordinary differential equations

PDE: partial differential equations

PK/PD: pharmacokinetic/pharmacodynamic

PrioMed Child: priority medicines for children

RCT: randomized controlled trials

Introduction

Drug development is a long – often more than 10 years – and costly – more than 1 billion Euros each – machinery [1-3], requiring experiments in animals and humans. More recent alternative approaches, such as computer modeling and simulation (M&S) provide supplementary tools for developing drugs [4-8]. These M&S approaches, successfully applied in a variety of industries (aircraft and car manufacturing, nuclear power plants, etc.) will represent a major paradigm shift and factor of progress in a close future for drug development. EU Avicenna roadmap [9], and FDA recent position [10] are important signs of these coming changes.

Such an approach may be of particular interest in the field of rare diseases where conducting clinical trials may be very challenging and the level of available evidence from clinical studies remains insufficient. Recently, the CRESim consortium [11] tested whether *in silico* clinical trial simulation could help to choose the most appropriate design for drugs in three rare disease situations. The results of this M&S program have however to be further discussed and some additional perspectives can be proposed for future research in this field.

Specificities of orphan drug development

There is a need to facilitate the development and availability of high-quality, ethically sound, and appropriately authorized medicines in rare diseases, without subjecting patients (especially children) to unnecessary trials [12, 13]. Conducting adequately powered randomized controlled trials (RCTs) may not be possible because of the small number of potential participants. Small clinical trials have a low statistical power and also lack of generalizability. New approaches are needed for designing valid trials with small sample sizes that can assess the potential therapeutic effect of drugs, biological products, medical devices, and other medical interventions. Therefore, the aim of the CRESim program was to propose a generalizable strategy utilizing datasets analysis in combination with modeling and simulation, in order to optimize the clinical drug development in the field of rare diseases.

The CRESim program

The “European Child-Rare-Euro-Simulation” project (CRESim project no. 40-41800-98-008) was funded in 2011 by the European Union’s ERA-Net PrioMedChild (priority medicines for children). Briefly, the main objective was to investigate and compare RCT designs for drug evaluation in children with rare diseases using *in silico* experiments (i.e. RCTs modeling and simulation). For demonstration purposes, three diseases were studied: Dravet syndrome (myoclonic epilepsy in infancy), cystic fibrosis, and T-cell lymphoblastic lymphoma. Several RCTs designs have been modeled, i.e. the parallel-group, cross-over, randomized withdrawal, early-escape and N-of-1 trial designs. Various performance criteria were simulated for comparison purpose in terms of: 1) trial durations, this criterion represents the ‘burden’ of the trial for the patient, the investigator and the sponsor, and 2) precision of the estimation of the treatment effect, a criterion evaluating the “performance” of the trial. Eleven scientific articles referenced in PubMed [14-24] showed the feasibility and the interest of such an approach. The successive dimensions that were considered are described in Fig. 1.

Basic principles

For each disease of interest, up-to-date biological and biomedical knowledge must be synthesized through mathematical models to simulate 1) the function of one or several systems in human (and possibly in some animal species), their dysfunctions leading to one or several components of the disease, and 2) the impact of current (in the same indication or in repositioning, i.e. in a new indication -rare disease especially-) and new treatments on these dysfunctions [19, 22, 25, 26]. Such a process results from a close collaboration between relevant disciplines: applied mathematics, computational modeling, systems biology and pharmacology, pharmacokinetic and pharmacodynamic modeling, clinical pharmacology and medical specialities. Drug safety has also to be taken into account as far as possible, in order to assess a net clinical benefit [27].

Existing and new mathematical models are developed to capture variability of *in vivo*

parameters and system(s) functioning, in individuals, female and male of different ages (children, teenagers, young and mature adults, elderly). This development is possible through retrospective databases analyses and/or specifically devoted prospective cross-sectional studies of healthy volunteers and patients.

Using these mathematical models realistic virtual individuals and populations will be generated and will be randomised in virtual clinical trial simulations [28]. These populations are called “realistic” because of the similarities between these virtual individuals and real individuals, their ability to simulate and predict biomarkers evolution and/or the occurrence of some clinical endpoints in patients [29,30] and to reproduce the therapeutic impact of drugs.

Validation process of mathematical models remains a key issue and must involve several aspects: 1) Usual internal validation process for model building: the model is built with a set of available data, and validated using a separate set of data from the same database; 2) Confrontation of predicted and observed results of specific biomarkers in human cohorts of diseased patients; 3) Ability of the model to predict results from already performed clinical trials (if any) in terms of clinical events, in both treatment groups (placebo and tested drug); 4) possibly, ability of the model to explain discrepancies between animal and human experiments.

Proposal for specific points to consider

Databases

Depending on the existence of clinical databases, the corresponding strategy could be considered as follows:

- Using existing clinical databases (epidemiological and RCTs databases if any), their use is necessary for: 1) Identifying prognostic and predictive biomarkers: prognostic biomarkers are biomarkers which are linked with a specific favourable or unfavourable evolution of the disease, and predictive biomarkers are associated with the response of patients to specific drugs; the validation of a predictive biomarker requires specific statistical approaches [31, 32]; 2) Constructing realistic virtual population(s) of patients: sets of virtual patients are matrixes of

variables and covariates representing individuals; they are realistic when the interrelations between variables are controlled to realistically mimic patients (using parametric methods and/or resampling techniques and/or Bayesian networks); 3) Model validation: the validation process includes an internal validation (with the use of a training set), temporal validation [evaluation of the performance of a model on subsequent patients from the same centre(s)/dataset], an external validation [i.e. generalizability of the model by testing the performance on other centre(s)/dataset] and sensitivity analysis (the study of how variability in the output of a model can be attributed to different sources of variability in the model input [33]).

- If appropriate, generating new prospective cross-sectional studies involving healthy subjects and / or patients for: 1) Identification of numerical values of model parameters; 2) Assessment of intra and inter-individual parameter variability; 3) External model validation (replication of biomarkers results using specific individual patient characteristics).

Progressive and integrative model building

This step is a way to incorporate each new piece of information in a relevant edifice. Mathematical language enables prediction and establishing dynamic links between: 1) Inputs, such as drug dosage, route of administration, posology, treatment duration and patient compliance to the drug regimen [34–37]; 2) Individual characteristics that modulate the relationships as covariates; 3) Relationships between entities such as dose and concentration, concentration and effect on biomarkers/surrogate outcomes, impact of biomarkers on final clinical outcomes. These mathematical models are initially simple and become more and more sophisticated and accurate when incorporating more information. They become sometimes more complex, to take into account: 1) Specificities in drug distribution with several virtual compartments, or more numerous compartments mimicking the reality of different organs in which drug diffuses (physiology-based pharmacokinetic models) or 2) Several biomarkers/surrogates resulting in indirect and/or delayed effects, or a chain of causal mechanisms, or feedback loops mimicking counter-regulation mechanisms. They become also more and more fit to individual profiles, in order to capture the different characteristics that explain the between individual variability.

Modeling steps

The modeling process consists in:

- Construction of specific (sub)models for: 1) Disease(s) characteristics/spontaneous evolution using statistical and/or mechanistic models [most often ordinary differential equations (ODE) and/or partial differential equations (PDE) systems]; 2) Drug(s) effect(s) [38] using pharmacokinetic-pharmacodynamic (PK-PD) models [39, 40, 41]; 3) RCT characteristics (experimental designs [42, 43, 44]) and their corresponding statistical methods of analysis (e.g. frequentist versus Bayesian approaches [45, 46], parametric versus non parametric approaches, meta-analysis).
- Prospective validation of the disease and drug-effect models (model verification and validation, comparison between predictions with observations, sensitivity analyses).
- Connection of submodels together into a meta-model for simulation purposes.

RCTs modeling

This dimension involves:

- RCT simulation using: 1) An input-output (IO) submodel; 2) A covariate distribution submodel; 3) An execution submodel; 4) A specific statistical analysis according to each considered design; 5) An additional exploratory search for predictive biomarkers.
- When required, (e.g. in ultra-rare diseases), simulations of cohorts of virtual patients can be performed for: 1) Formal external indirect comparisons approaches; 2) Investigation of new prognostic biomarkers of potential interest; 3) Construction of prognostic scores for model calibration purposes.

Simulation strategies

This results from exposing realistic virtual populations to a variety of simulated clinical trials with a considered drug. The drug impact is directly observed from the comparison of the disease evaluation in the same population simulated after drug or placebo exposure. A large number of scenarios regarding RCT designs, drug dosages, drug associations, selection of patients, length of exposure, etc. can be explored through this approach. The main steps are as follows:

- Samples of patients randomly drawn from the ‘validated’ virtual population for inclusion in *in silico* RCTs.
- Applying a pre-specified simulation strategy to optimize and limit the number of simulations.
- Use of the same specific statistical analysis for each simulated RCT results.

Simulation results analysis

A multidimensional analysis must be finally performed to put into perspective the simulation results. At the end of the simulation process, an example of the expression of results is given below:

- the median of the estimations of the treatment effect and the medians of the lower/upper limits of their 95% CI;
- an evaluation of the precision of the estimation of the treatment effect, e.g. the coefficient of variation (corresponding to the ratio between the standard deviation of treatment effect and the corresponding median).

The corresponding graphical representation may use for example the radar plot approach. Each axis of radar plot represents an evaluation of one component of interest. The furthest value from the center corresponds to the ‘ideal’ value for clinical trial, e.g. a high power (%), a low variability (%), a short patient duration (days), short investigator and sponsor durations (years), and a high number of patients under active treatment.

Other possible applications of simulation

Their main interest is to compare results from real RCTs with the results from simulated similar RCTs that would have been designed if the mathematical models were available and used. In addition, case studies can specifically assess the potential of the innovative approach to achieve better level of evidence at lesser costs, to reduce the number of human (and animal) test-subjects, e.g. through optimising experimental design, or explaining and preventing failures in drug development.

Comprehensive overview of the overall process

The global process may be summarized in Fig. 2 that includes the simulation of a virtual population of patients (modeled from a real dataset of patients), the modeling of disease components and PK-PD of the drug of interest, the modeling of several RCTs designs and the analysis of the results (multi-dimensional approach for RCTs durations and precision of the estimation of the treatment effect).

Limitations

Some possible barriers have to be mentioned and further taken into account:

- conservatism of pharmaceutical industry, regulatory bodies, pharmacologists, methodologists and physicians;
- need to involve different disciplines that do not work usually together;

- time consuming nature of the process (results are not ‘handy’ and their integration into the development plan is still not well defined);
- the cost-effectiveness of the modeling approach should be demonstrated;
- the regulatory framework has to be better defined.

Perspectives

Recent advances in *data sharing* and in clinical trial methodology offer new perspective to clinical trial simulation. The development of databases which are either open access or on demand access facilitates formal indirect external comparisons for prediction issued by modeling, and building datasets of virtual patients who become more and more realistic.

Similarly, *biomarkers* previously identified using bioinformatic approaches could be first validated in silico.

The same approach could allow the in silico evaluation of the interest of coupling therapeutic and diagnostic (*theranostic*) strategies.

Extensive use of databases could allow the application of specific *enrichment strategies*, i.e. the selection of patients whose characteristics are likely to optimize the chances of success of a trial. This strategy could also be applied to the field of rare diseases whenever possible [47, 48].

The application of modeling and simulation in the field of *4P medicine* (predictive, personalized, preventive and participatory) offers the perspective for each new patient to have the results of a given trial reanalyzed according to his/her own characteristics / preferences (e.g. interest of use of generalized multiple pairwise comparisons for trial re-analysis [49, 50]).

Academic and industrial partners should have free access to dedicated *RCT modeling and simulation platforms*.

Conclusion

M&S will speed the availability of well documented drugs on the market, positioning adequately new drugs. It has the potential to reduce costs of drug development, including the number of needed individuals to be recruited in clinical trials, by avoiding useless trials and optimizing precision through trial designs [51–54].

All stakeholders (regulators, academics, firms, patients associations) should be involved as soon as possible in each new research program to allow their expectations to be taken into account, and in return to be informed on the program advances and for regulators to prepare guidelines.

Lastly, whereas M&S results obtained from simulated RCTs performed in ‘virtual’ patients can improve the methodological approach of drug evaluation in the field of rare diseases (particularly in children), they cannot be considered as substitute for RCTs performed in ‘real’ patients.

Disclosure of interest

Authors have no competing interest to declare.

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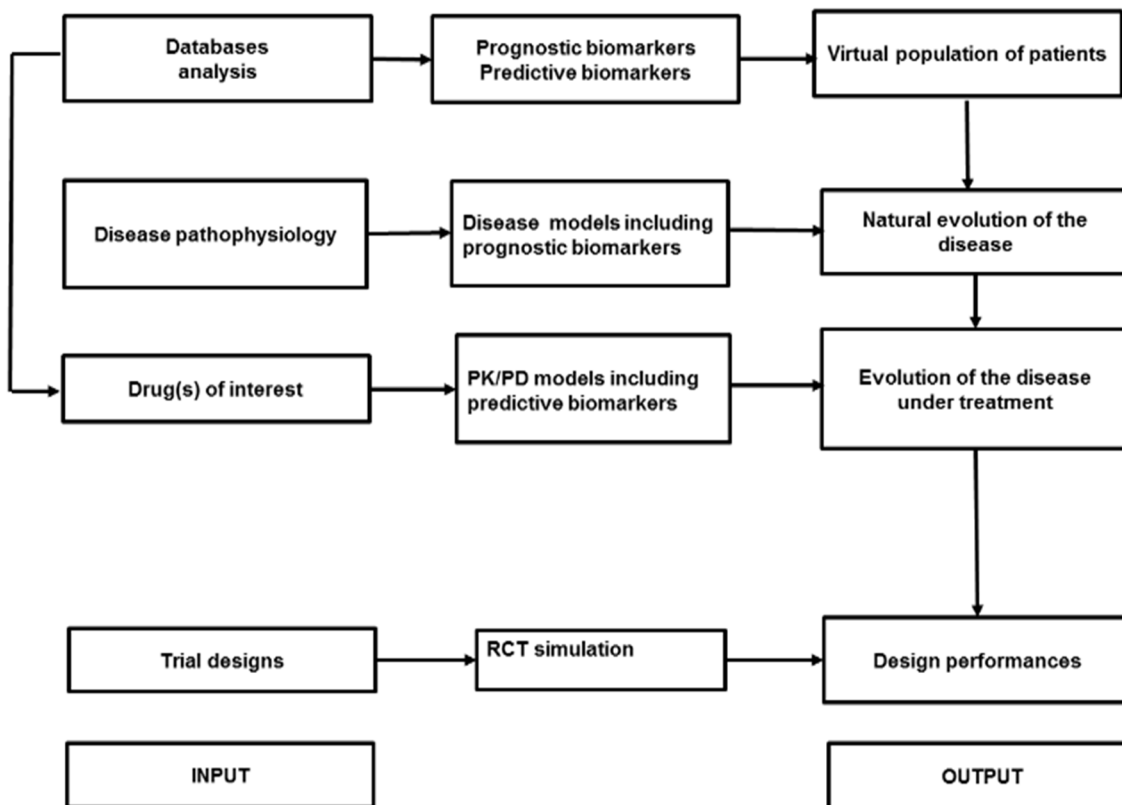
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Figure 1. Modeling steps for RCT simulation.

Construction of a virtual population of patients from epidemiologic databases, modeling disease prognosis and therapeutic effect from pathophysiology and PK-PD relations, RCTs simulations using different experimental designs, comparison of design performances

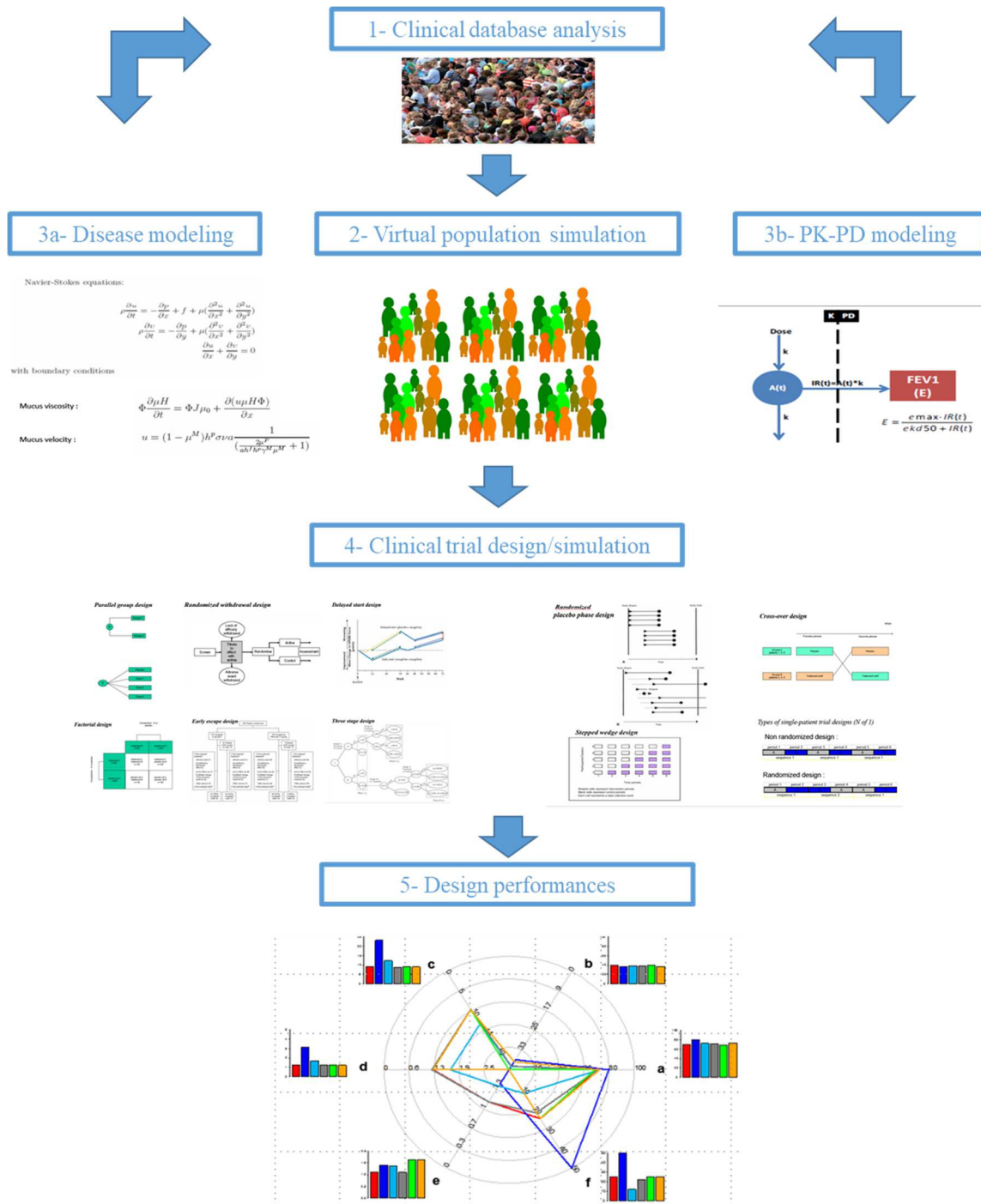


PK/PD: pharmacokinetic/pharmacodynamic; RCT: randomized controlled trials

Adapted from [16] Nony P, Kurbatova P, Bajard A, Malik S, Castellan C, Chabaud S, et al. A methodological framework for drug development in rare diseases. *Orphanet J Rare Dis* 2014;9(1):164. With courtesy Springer Nature (M Mohammad Suleik).

Figure 2. Flow diagram of the overall process.

Using data of a real population of patients (1), a virtual patient dataset is built (2) and connected with a disease pathophysiological model (3a) and PK-PD models of drug(s) of interest (3b). Samples of virtual patients are randomized in virtual RCTs with different experimental designs (4). Simulations results are compared using a multi-dimensional approach (5).



PK/PD: pharmacokinetic/pharmacodynamic; RCT: randomized controlled trials