"In Silico Clinical Trials": a way to improve drug development?

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Abstract
Many clinical trials are negative or inconclusive. Thomas Burns estimates to 42 % the proportion of Phase III trials which fails to meet the primary objective in the period 2006-2015 [27]. The causes of such failure are numerous. Obviously, there is the lack of effect of the treatment under study, a cause which cannot be anticipated. But there are other causes related to trial design and trial operation that can be avoided or at least challenged by means of simulation studies. The aim of In Silico Clinial Trials (ISCT) is to test the feasibility of an experimental design and to evaluate its sensitivity to a modification of the design parameters. By this way, one can optimize the trial design by anticipating what can happen during the trial. The purpose of this paper is to outline what an ISCT may be and to focus on the methodological pillars of this approach. Issues on the development of ISCT will also be discussed.

Key Words: Clinical trials, Simulation, Methodology, Agent-based model

1. Introduction

Clinical trial is a major component of medical research and drugs development. It is nevertheless a particularly challenging process essentially for scientific and economic reasons. Scientific because clinical trial is a long process strictly supervised by a research protocol during which science goes on. Economic because clinical trial is an expensive process. This economic issue is of paramount importance for pharmaceutical Companies. Focusing on phase III trials, the Pharmaceutical Research and Manufacturers of America estimated the cost at $42,000 per patient in 2013 [6]. Much attention is (most of the time) paid to the management of these clinical trials, however a large proportion of the clinical trials fail. This leads to ethical issues regarding patient involvement [29].

Despite the regulation requiring dissemination of trial results, it is difficult to find information on non-conclusive trials. An explanation can be found in the poor proportion of trial following that regulation (68% of trials sponsored by pharmaceutical companies reported results within 12 months, for trials sponsored by universities, hospitals, government, and charities the proportion was 11% [8]). In the literacy, there are not so many studies dealing with the clinical trials failures especially evoking quantitative results. One of the more complete one is [10] from which is extracted Figure 1. This study shows that that around 70% of trial failures are due to efficacy and safety, around 5% are due to organization and the rest is due to commercial and strategic reasons. Only half of all drugs that are rejected during the process fail due to a lack of efficacy [6].

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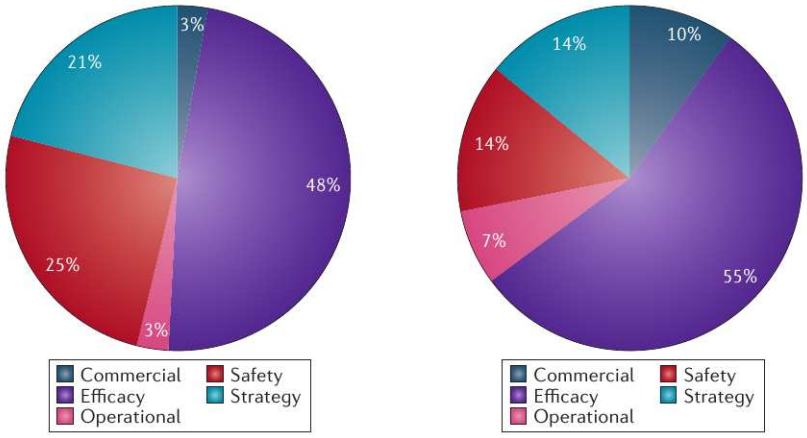

Figure 1: Reasons for failure in Phase II on the left and Phase III on the right clinical trials (from [10]).

Explanations of the causes of clinical trials failure are discussed in [6] and in various blogs (for instance [1, 4, 20]). Conclusions are more or less the same and yield to the following clusterization of the reasons of trial failure:

- Failure due to molecule activity issues,
- Failure due to design issues,
- Failure due to rational issues,
- Failure due to logistic issues.

Whatever the reason of the failure, those results have to be nuanced. Indeed, some causes can be studied or anticipated while others are not preventable.

Failure due to molecule activity issues comes from the lack of efficacy or lack of safety. In terms of efficacy, situations where a molecule does not have sufficient biological activity to make the difference between arms significant cannot be improved whereas a situation where the molecule has a a biological activity but that activity is not observed because it is not the expected one can be improved. In terms of safety, situation where there is severe and generalized toxicity, severe and unpredictable toxicity and severe and predictable toxicity (Exple: toxicity after a certain cumulative dose) are different, the first one cannot be improve while the third one can.

Failure due to design issues are common. One uses to say that a good design is based on the statement ”The right endpoint - The right dosing - The right patients”. That is closely linked with the timing of the trial, the placebo effect and disease progression and with patients recruitment. These points may be challenge in order to assess the impact of trial’s parameters to the endpoint. For instance patients recruitment which is of paramount importance in clinical trial confronted with the balance between the will to expand the targeted population to facilitate the recruitment and the necessity to shorten the targeted population to get a homogeneous population and to facilitate the highlighting of a treatment effect.

Failure due to rational issues means the reason of trial failure comes from weakness in the assessment of the current standard of care or weakness in the knowledge of disease area landscape.

Finally failure due to logistic issues comes from operations problems and flawed data collection/analysis [9, 20].

It is thus clear that many clinical trial failure may be avoided by an improvement of the clinical protocol (rational, design) or an improvement of operational activities of the trial. Let us quote Dr. Roger M. Mills who summarize the setting in [17] by "Good trial design cannot turn a poor drug into a good one. However, attention to good trial design does mean that a potential therapy will undergo a meticulous evaluation that clarifies its risks and benefits in the targeted disease state." The consequences of such an improvement might be huge: ethically (less patients included in vain), scientifically (less negative studies) and economically. Dr. Amar Thyagarajan says in [28]: "According to the FDA, drug developers could save $100 million in development costs per drug with a 10% improvement in predicting failures before clinical trials".

That is well known fact but the question of how to reach such an improvement is still of interest. A solution may comes from the introduction of simulation techniques in clinical research. For about thirty years, the use of simulation techniques have been introduced in drug development. The main idea is to use the huge amount of information available on the patients, on the drug of interest and on the design of the trial in order to build a stochastic model mimicking the course of the clinical trial. The strategy is to identify, in silico, design weaknesses, to measure the performance of a trial in a predefined setting while reducing the number of logistical barriers. The purpose being to make the most rational decisions possible regarding clinical development (see [25] and references). As early as 2009, the use of simulation techniques proved their benefits. In [3] Brindley and Dunn shown that simulations studies increase the probability of achieving objectives of the study, increase patient safety, reduce the duration of the study and the risk of protocol deviations and avoid inconclusive situations.

The introduction of simulation in clinical research seems natural but the literature does not confirm this idea. Indeed, the state of the art [11] relating to the period prior to 2000 and confirmed by the reviews [12] over the period 2000-2010 and [25] over the period 2010-2015 show little impact and use. Explanations of this paradox may be found in reporting bias, as such investigation may be conducted by pharmaceutical companies and not necessarily published for confidentiality reasons.

It is important to emphasize that the regulation agencies are boosting the use of simulation in drug development [19]. As an example, in 2011, the FDA released its strategic plan on Advancing Regulatory Science (`https://www.fda.gov/media/81109/download`). Four of the eight science priority areas evoked specifically call out modeling and simulation as important aspects of FDAs strategy. In the FDA Grand Rounds presentation of Dr. Tina Morrison[1] given on August 9, 2018 an overview of some current modeling and simulation methodologies were provided and the potential of in silico clinical trials were discussed (`https://collaboration.fda.gov/p4r7q3qweuv/`). Another example, during the last 10 years the European Medicines Agency (EMA) organized a number of workshops on modeling and simulation, working towards greater integration of modeling and simulation (M&S) in the development and regulatory assessment of medicines. In the 2011 EMA - EFPIA[2] Workshop on Modelling and Simulation, European regulators agreed to harmonize on good M&S practices and for continuing dialog across all parties. To do so, the EMA Modelling and Simulation Working Group (MSWG)

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[2] European Federation of Pharmaceutical Industries and Associations

has been established and the MID3 (Model-Informed Drug Discovery and Development) good practices paper publisehd in 2016 [15, 14].

Most of the simulation approaches are based on a compartmental definition of the virtual patients. By compartmental definition one means topdown model of human from submodels of whole organs to individual molecules. For example the HumMod project (`http://hummod.org/`) involves more than 1,500 equations and 6,500 variables (body fluids, circulation, electrolytes, hormones, metabolism, and skin temperature,...). Such complex models are very hard to handle and - even with such a large number of variables involved - often too simple essentially. Indeed, the strong dependence structure between variables, pillar of life diversity, is too difficult to take into account.

In contrast, a virtual patient is defined, in this paper, as a set of covariates essentially the ones involve in the clinical design (essentially inclusion / exclusion criteria) and the ones known to be linked with clinical outcomes of interest. This set is small enough to consider the dependence structure between covariates involved and to run properly the associated agent-based approach. The aim is sligtly different of the compartmental approach which aims to investigate, by silico, the behaviour of a patient exposed to a drug. Here, In Silico Clinical Trial (ISCT) is an agent-based model which the behaviour of a virtual patient in a virtual clinical trial. The aim is to challenge trial's design parameters in terms of feasibility and probability of success of the trial. In Silico Clinical Trial may be a relevant tool to challenge the trial in terms of risk of failure by investigating scenarios of trials according with the failure issues developed above.

The paper is organized as follows: Section 2 is devoted to the main steps of the construction of an In Silico Clinical Trial. Section 3 are some elements of discussion on what an ISCT may bring in drug development. Section 4 are some elements of discussion on the technical locks identified from our skill in this setting. Finally, paper closes with a concluding Section 5.

2. A General Schema of an ISCT

2.1 Generalities

As specified below, we define an In Silico Clinical Trials as the use of Virtual patients to mimic their behavior in a virtual clinical trial in order to challenge trials design in terms of feasibility and probability of success of the trial. An In Silico Clinical Trials can be thus be conceptualized involving various models:

- **The Virtual Patients' Generator**. This model aims to generate a dataset of virtual patients covariates stochastically. This dataset can be seen as the baseline data of a virtual patient included in ISCT. The constraints on this model can be summarized in two points: to be consistent with the protocol we aim to investigate, to be well balanced between complexity of the model and realism of the virtual patient.

- **The execution models**. Execution models are input/output models which aim to complete or to modify the virtual clinical dataset. Various execution models can be considered. On Figure 2, an example is given involving an execution model which complete the dataset with virtual outcomes at different times and an example of execution model which modifies the dataset introducing adverse events.

Figure 2 is an example of what may be the simulation's schema of an ISCT. Details and much more sophisticated ISCT involving other execution models are discussed in the two

following subsections.

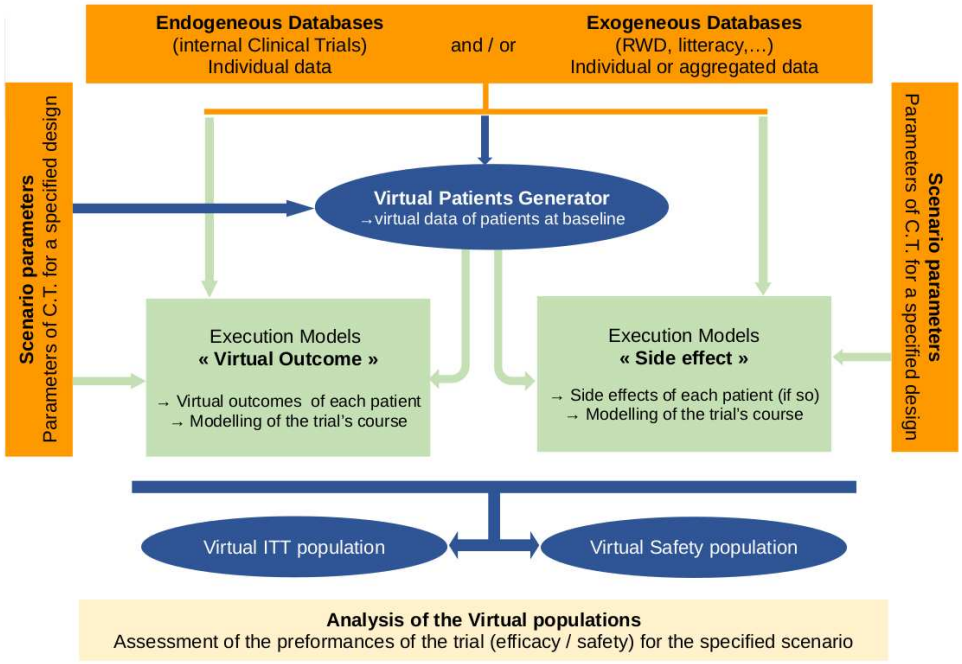

Figure 2: Example of the simulation designs schema of an ISCT.

2.2 Virtual Patients Generator

This first step of an In Silico Clinical Trial consists in the generation of baseline data of virtual patients involved in the virtual trial. Virtual Patients Generator involves essentially Monte Carlo generation of a vector of covariates (see, for instance, [21, 22] for details). The two constraints on the model are:

- The marginal distributions are consistent with the ones of the population of interest.
- The correlation structure between covariates is consistent with the one of the population of interest.

The constraints on the marginals is not a big deal but things are much more difficult to achieve the second constraint. When the parameters of the distributions are known, the, usually named, Discrete method is exact. But most of the time these parameters are estimated from data and Discrete method is less effcient especially when there is a large number of covariates mixing continuous and categorical ones. The so-called Continuous method introduced in [26] to generate database directly from the population parameters, may be a good alternative but most of the time it is a too simple model especially when there is a multi-modal distribution. Copula's method is probably a good alternative as specified in [25].

The main advantages to consider virtual patients are: first, a virtual patient is a "good guy", perfectly adherent to what one wants him to do, no ethical problem, no problem with "General Data Protection Regulation", second, a virtual patient is able to follow various

treatment arms at the same.

The main disadvantages to consider virtual patients are: first, a virtual patient will always be much more simple as a real patient, second, many covariates have to be included to get a realistic patient and accounting for correlation is rapidly a strong problem to deal with. This question will be discussed in much details in Section 4.1.

2.3 Execution Models

An execution model is an Input / Output model which aims to simulate the course of the virtual clinical trial (see Figure 2.3 for schema of a general execution model).

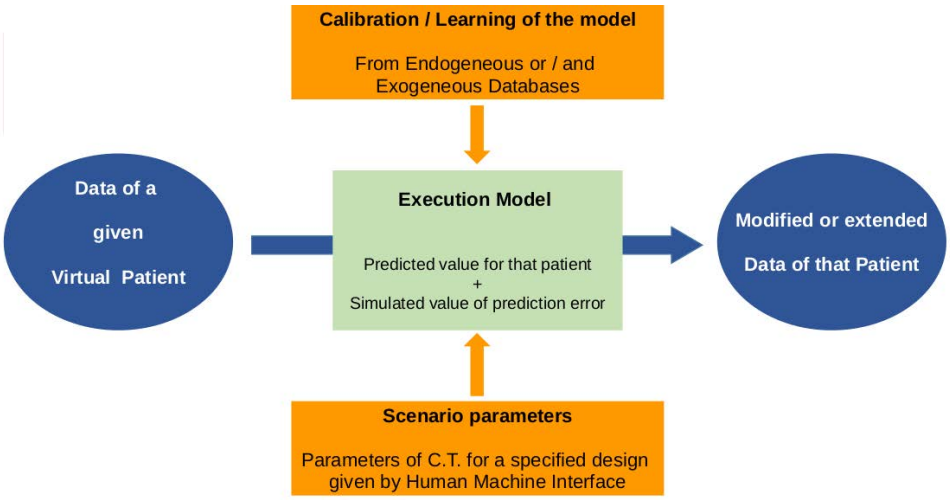

Figure 3: General schema of an execution model.

Many execution models can be considered making the ISCT more complex but probably closer to reality. It is important to notice that execution models are dependent in the sense that the input of a model may refer to the output of another model. The hierarchy of the models has to be thought properly. Here are some example of execution models that can be involved:

- Baseline's parameters evolution in time (an example is given in [24]),
- Virtual outcome generator,
- Disease progression model [5],
- Side effect model, drop-out model,
- Recruitment model [16, 18].

To insure the versatility of the construction of an ISCT, each model may be improved separately. This property is known as the modularity and is a property of major importance for ISCT building and improvement.

There is a wide variety of models available as candidate for execution model: parametric models such as Markov Process, Cox process, regression model, Bayesian network,...

and non-parametric models such as machine learning techniques (Random forest, XG-Boost, Decision trees, SVM, deep learning,...).

Those models depend on parameters that can be split in three categories: parameters linked to the patients, parameters linked to the model (tuning parameters) and parameters linked to the design. Those parameters can be considered as punctual (deterministic) values or as distributions (random) in a Bayesian's paradigm. Parameters can be fixed by the user or estimated from databases. Parameters fixed by the user, by means of a Human Machine Interface, state a scenario which define the conditions under which the trial is followed. Parameters estimated from databases are calibration parameters which are fixed during the simulation.

The output of an execution model comes from a Monte Carlo simulation accounting for the model chosen and for the values of whole the parameters involved. It is important to keep in mind that the aim of an execution model is to simulate an outcome and not to predict an outcome. That is an important point because it is stronger, it necessitates a model not only with good predictive performances but also a modeling of the error of prediction. Figure 4 is an illustration of the error made by considering only predictive properties. On the first row are plotted the histograms of XA and YA together with the plot of $(\mathrm{XA}, \mathrm{YA})$ those data are considered as a historical database ($n = 80$). From $(\mathrm{XA}, \mathrm{YA})$ is constructed a predictor which is a simple regression model. On the second row data XP are 1000 generated values from a Gaussian fitting of the XA's. YP are the predicted values given by the linear predictor. The plot $(\mathrm{XP}, \mathrm{YP})$ is a straight line which is not consistent with the reality. On the third line, an error term has been considered by adding to the predicted value a Gaussian residual whom standard deviation is estimated from the historical data. It is easily seen that the plot $(\mathrm{XP}, \mathrm{YS})$ is much more realistic that $(\mathrm{XP}, \mathrm{YP})$.

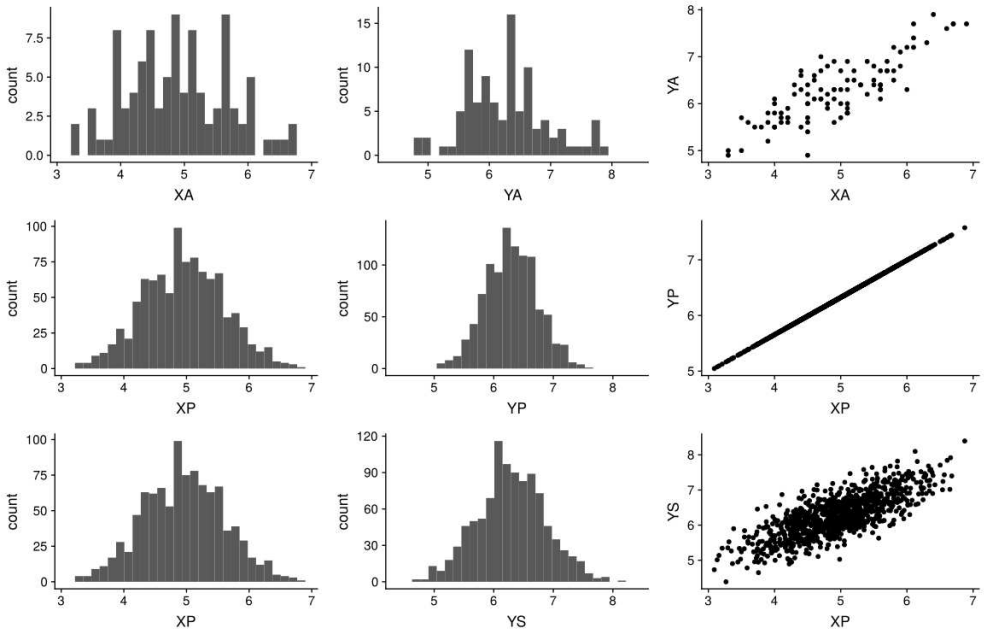

Figure 4: Illustration of the error made by considering only predictive performances. On the top the learning data, in the middle simulated abscissa and predicted ordinates, on the bottom simulated abscissa and simulated ordinates.

Notice that the confusion between prediction and simulation yields to an under estimation of the error and thus it is easier for a factor effect to be significant.

3. What an In Silico Clinical Trial may bring to drug development?

3.1 Perform sensitivity analyses of Clinical Trial endpoints

In Silico Clinical Trials allows to perform sensitivity analyses of clinical trial endpoints. To do so, it is possible to assess the performance of the trials as a function of parameters by varying the feature of the patients, the parameters of the design and parameters of the execution models. Indeed, it is possible to:

- Modify the feature of the patients, this means to challenge the inclusion / exclusion criteria of a trial, by modifying the marginal distributions of the baseline covariates in the virtual patients generator,
- To specify design parameters (for example duration of patients' follow-up, number of centers involved,...) by specifying various scenarios, this means various set of parameters in execution models, and by assessing the related trial performances.
- To assess the impact on the trial performances of small changes in the values of the parameters of the execution models (for instance quantify the impact of a given variation of patients' recruitment rate on the trial duration).
- To explore the trial performances for untested values of the parameters of the execution models (for instance what would be the consequences on the performances of a trial in which a patient is followed one year if it is reduced to six months).

It is important to point that these two last strategies are much more easy to investigate with parametric models for execution models than non-parametric models.

3.2 Perform performances analyses of a predefined trial.

In order to demonstrate that the difference observed between treated and untreated patients is due to the intervention (the treatment), an usual way is to assess the Average Treatment Effect (ATE) defined as:

$$\mathrm{ATE} = \mathbb{E}\left[Y(1) - Y(0)\right]. \tag{1}$$

where for patient i, $Y_i(1)$ is the outcome for patient i treated and $Y_i(0)$ is the outcome for patient i untreated. $Y_i(1)$ and $Y_i(0)$ are known as potential outcomes [23] and in practice, both these values cannot be observed simultaneously and ATE cannot be estimated properly. The Average Treatment Effect is usually estimated by

$$\hat{\mathrm{ATE}} = \frac{1}{n_A}\sum_{i=1}^{n_A} Y_i^A - \frac{1}{n_B}\sum_{i=1}^{n_B} Y_i^B$$

where $(Y_i^A, i = 1, \ldots, n_A)$ (resp. $(Y_i^B, i = 1, \ldots, n_B)$) is a sample of patients treated (resp. untreated). In the setting of a randomized trial, the quality of this estimation is rather good up to unmeasured confounded factors.

In the context of an ISCT, virtual patients can explore both treatment arms and the performances of this predefined trial can be assessed since ATE can be estimated directly from (1) by:

$$\hat{\mathrm{ATE}} = \frac{1}{n}\sum_{i=1}^{n}(Y_i(1) - Y_i(0)).$$

4. Main issues in ISCT building

4.1 Issues in Virtual Patients Generating

The issues linked to Virtual Patients Generation are the usual ones of Monte Carlo generation for multivariate distributions (see [13]). The constraints are listed in Section 2.2 and the problem is to found a balanced between details of the virtual patients and complexity of the model involved to generate such patients. The problem is magnified by the type of distributions involved which can a mix of categorical and quantitative variables.

The complexity of the model depends on the number of covariates. It is therefore important to have a clear approach to selecting variables including data and expert knowledge. Once data selected, the issue is to to calibrate properly the model. Many problems arise: First, in this context of multi-dimensionality, the dimension of the database used to make the inferences is of major importance. That is linked with the curse of dimensionality which indicates that the number of samples needed to estimate an arbitrary parameter with a given level of accuracy grows exponentially with respect to the number of input variables. Second, the origin of the data is of importance too because the data do not have the same quality depending on whether they are derived in randomized trial or real life data. Third, if there is no (or not enough) data available for inferring the Virtual Patients Generator, it is always possible to fixed the values of the parameter and to perform sensitivity analyses. In this case, it is important to clearly specify the assumptions made on the model.

4.2 Issues in execution models calibrating

A huge diversity of models may be considered for the execution models: parametric models (Markov, Cox, linear, logistics,...) and non-parametric models (Machine learning). The main difference between those two approaches is parametric models calibrate by means of data and assumptions while non-parametric models are completely data-driven. Many sources of data may be used: completed clinical trials, on-going clinical trials, real-word database with really different levels of quality and levels of accuracy. The quality of the execution model may be very different according to the database used for calibration.

For parametric models, the main issue comes from the data used for parameters estimation. The results are better with large databases since inference is better but if there is no (or not enough) data available it is still possible to make stronger assumptions on the model to simplify it. The other advantage of parametric model is the possibility to use data from literacy, from expert knowledge or fixing a value and perform sensitivity analysis.

For non-parametric models, the main issue comes from the fact that there is no alternative to the data-driven approach. Without data it is not possible to consider a model and with data, the model is much more sensitive to it quantity and to the structure of the database. Indeed, the quality of the prediction is linked with the structure of the database, the model learn from the data explored, if the database do not explore certain values, the prediction associated with such value will be poor or not available. For instance if there is no information in the learning database on young people (< 30 years old), the predictor will not predict anything for young people.

Whatever the nature of the model a recurring question is the portability of the data. Indeed, is it realistic to learn a model (parametric or not) from a dataset involving patients completely different of the patients to include in the ISCT (for instance learn from American people for an European study). To overpass this problem, various algorithm such as OT-algorithm [7] may be of interest.

Finally, the most important point to catch is that execution models aim to simulate an outcome and, as pointed in Section 2.3, it necessitates to model the error of prediction to

properly simulate the outcomes.

5. Conclusion

In Silico Clinical Trials will never replace clinical trials with real patients. Indeed, virtual patients will always be too simplistic for giving values to an outcome under experimental treatment but enough specific to compare scenarios. Thus, In Silico Clinical Trials suggests, first, by challenging trials' designs, an increase of the probability for a trial to be conclusive and, second, by considering simulated values under placebo, the possibility to develop the design of new trials much more ethic (digital twins).

This paper has pointed that most of the tools are now available, the methodology has been properly thought and rests on four pilars [2]:

- Clarity: The report of the simulation should be understandable in terms of scope and conclusions by intended users.
- Completeness: Assumptions, methods and results have to be described with enough details in order to be reproduced by an independent team.
- Parsimony: Complexity of the model and simulations procedure have to be no more numerous that necessary.
- Modularity: Each sub-model can be improved independently of the others.

However many challenges remains especially methodological ones: how to generate relevant virtual patients? how to build relevant execution models? how to calibrate or train those models? and technical ones: how to identify the right data? how to access the right databases? how to exploit properly those databases?

To conclude, In Silico Clinical Trials is a fantastic opportunity and is probably the future of drug development. There is still a lot of work to make the ISCT operational but the revolution is under way.

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