

Based in Geneva, Switzerland, *Data Mining International* is a leader in advanced analyses for databases, as well as small sample significance management, multicriteria analysis and clinical data rescue. Company CEO Ariel Beresniak is an MD specialising in Public Health. *OrphaNews Europe* asked Dr. Beresniak to discuss the particulars of managing data in studies for rare disease medicinal products.

OrphaNews Europe: *As CEO of Data Mining International, a leading company specialising in statistical and mathematical analyses of clinical databases, what is your opinion on the need for specific clinical analyses for orphan diseases ?*

Ariel Beresniak (AB): We are observing today some important changes in the clinical development environment. Relying on well-established policies and processes dating from the 1960s, clinical assessment is based on theoretical foundations that do not meet the needs of the challenges facing modern science today. The development of the biotech sector is one response to the changing expectations of patients, doctors and public authorities.

These expectations can be summarised in 3 points :

- better management of chronic diseases
- development of efficacious products for rare diseases
- quick availability of innovative products

It is not enough that an innovative product be potentially safe and efficacious, it is necessary to be able to demonstrate this. The principle of clinical assessment demands planning a clinical study as large as the efficacy differences are expected to be small.

Current calculations of the number of subjects needed for one trial are often not compatible with acceptable budget and time duration constraints, and are also quite impossible in terms of patient recruitment feasibility. Orphan drugs are often developed by the biotech sector, which specialises in niche markets. In addition, most clinical trials cannot reach the significance threshold (p value $< 5\%$, meaning that we accept a 5% risk of error), jeopardizing the potential access to market for tested products.

OrphaNews Europe: *Are there any potential solutions to the lack of statistical power of clinical trials in rare diseases?*

AB: The lack of power of rare disease clinical trials is not a fatality. A non-significant clinical result can have two main causes: either the product is not efficacious enough or the number of subjects is too small.

In order to know if the lack of significance is due to lack of product efficacy or the lack of subject numbers, it is firstly possible to use statistical techniques particularly adapted to small samples. Most of these statistical tests belong to the non-parametric test family and are regularly used because there is no requirement for a “normal” distribution (usually observed in large samples).

We can also use simulation techniques such as “re-sampling” techniques which are based on random generators, in order to “clone” the master sample in several thousand derived samples. These techniques, derived from “Monte-Carlo” techniques, are frequently used in operational research and in financial modelling and can be associated with non-parametric tests to establish potential significant results when classical approaches have not been able to do so. The coherent and appropriate use of these techniques could then allow to “reanimate” some clinical results previously considered “non significant”.

OrphaNews Europe: *What about the credibility of simulation techniques?*

AB: Most people forget that a clinical trial is always speculative. A clinical trial is an experimental model assuming that results could be applied to a patient population with the same inclusion and exclusion criteria. Usually, the real population is quite different from the clinical trial population. If theoretical conditions of models are well understood, results from simulations could be scientifically very robust.

Numerous domains outside life sciences use simulation techniques: insurance, telecom, air and space, environment, et cetera. The biggest liner-airplane in the world, Airbus A380, performed its first flight without any aerodynamic tests in real scale - thanks to aerodynamic modelling! Life sciences are definitely uncertain, and thus speculative. Simulation techniques using engines such as random generators are able to simulate a distribution of uncertain events in life sciences. Only these techniques can generate relevant information from small populations, and thus obtain potential significant results from small clinical trials.

OrphaNews Europe: *Despite important potential needs, why is it that advanced statistical analyses and simulation techniques are still rarely used in clinical trials?*

AB: The right understanding of the issue raised by the clinical experimentation, along with the refined skill of statistical sciences, mathematics, and applied information technologies are necessary together to carry out a smart and complete advanced analysis plan, and to define the base of a simulation model. These skills are rare and diluted in every scientific area. Furthermore, statistics departments in the pharmaceutical industry are nowadays very “protocolised”: repetitive statistical requests on standardised statistical software without any prior methodological discussions. This area has not really evolved in 20 years and is becoming non-adapted to the need of more “tailor made” studies in rare diseases.

OrphaNews Europe: *Do regulating authorities such as the EMEA and FDA recognise advanced statistical analyses and simulation techniques?*

AB: Neither the EMEA or FDA seem to impose closed lists of “authorised” methods and “non authorised” methods. These authorities usually privilege discussion and method transparency, even if the dialogue is sometimes not very easy from the point of view of the pharmaceutical industry.

Our recommendation would be not to substitute classical statistical analysis with sophisticated techniques, but to complete it. This would give regulatory authorities more complete information with which to enrich the decision-making process.

On the other hand, FDA experts are perfectly aware of the limits of classical clinical assessments, particularly in rare diseases. Internal working groups in orphan drugs exist and very probably new guidelines for statistics and modelling will be issued very soon. Preliminary recommendations in pharmacogenetics were already published in 2005 (*Pharmacogenetics - Toward improving treatment with medicines*, CIOMS, Geneva 2005) by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the WHO, FDA and EMEA. These recommendations include the use of simulation models.

OrphaNews Europe: *How do you see the future of clinical trials for rare diseases?*

AB: For ethical reasons, as well as budget, timing and recruitment feasibility, we will very probably observe the development of more small clinical trials with very precise targets on which it will be possible to plug various modelling and simulation techniques.

However, the quality level of these trials will be very high, not only for the methodological design, but also for the monitoring. Strong efforts will be made to minimize the risk of missing data and to improve patient compliance during the trial. These will be the conditions under which it will be possible to extract highly relevant information from small populations.

OrphaNews Europe: *Can you describe the “modelling”, “re-sampling”, “bootstrap”, and “Monte Carlo” techniques in terms their applicability to rare disease and orphan drug studies?*

AB: Modelling is an approach using mathematical language in order to link parameters with a mathematical formula - the “model”. A model can complete an experimental study because it is able to calculate the value of some unknown parameters from some known parameters. The aim of the Monte-Carlo technique is to generate data dispersion by using random numbers. It can be applied to large populations and often used in this case to test the sensitivity of some models (impact on the results after changing some parameters).

Re-sampling techniques (Bootstrap or Jackknife) belong to the Monte Carlo approach, applied to small samples. They consist of declining the original sample in a number of derived samples in order to create a new parameter distribution that could be tested with relevant statistical tests. Re-sampling techniques are particularly adapted to rare diseases by magnifying small treatment differences.

OrphaNews Europe: *How can the “decision-making approach” be useful to rare disease clinical trials?*

AB: Clinical trials are classically based on the “explicative approach”, comparing one single parameter (the primary endpoint) between two (or more) treatment groups. The question is: Which treatment group has the best primary endpoint?

The “decision-making approach” allows for the possibility of performing the assessment based on several endpoints. The question is: Which treatment group would we like to choose? Modelling techniques are often designed in the framework of the decision-making approach because the final objective is to support the decision.

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