ERA-NET PRIOMEDCHILD

Predicting the best way to test new drugs

Computer modelling can be used to find the best method of performing a clinical study on a new drug. Finding the optimal study design is especially important when testing drugs in children with rare diseases, so as to minimise the research burden on these young patients and optimise the chances of finding effective and safe treatments. 'People use mathematical models to develop a new aircraft, so why not use these techniques to improve drug testing in children?', says dr Catherine Cornu, co-coordinator of the CRESim ('Child-Rare-Euro-Simulation') project.

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Millions of children across the European Union suffer from rare diseases such as cystic fibrosis, neurological syndromes or rare forms of cancer. It often takes quite some time before a definitive diagnosis can be made, there's much uncertainty about the prognosis and most importantly, there may be no treatment available. Fortunately, during the past decades there has been an increasing awareness of the need to do something about these so-called 'orphan diseases'. In both the United States and Europe, there is now legislation and funding aimed at the development of effective treatments for rare diseases. These developments provide hope to children with rare diseases and their parents.

Like any other drug, orphan drugs must be tested to make sure they are effective and safe, before being authorised for use on the European market. This can be difficult, because the low numbers of patients with rare diseases may not allow for the traditional model of clinical drug trials, the Randomised Controlled Trial (RCT). In a randomised control trial, patients are assigned at random to a study group or a control group. The study group receives the new treatment, the control group the usual treatment. Following the study period, the outcome in both groups is compared. Statistics show that to achieve results with sufficient certainty, relatively large groups of patients are needed, often as many as several thousand. So what can be done when there are not that many patients? Will another study design predict efficacy and safety with an acceptable amount of certainty? And how can we know in advance which study design provides the best guarantee that a trial will produce reliable results? Computer modelling may prove to be the essential tool here.

Pooling expertise

The PRIOMEDCHILD project tries to find new methods of studying the safety and efficacy of drugs, in a more tailor-made fashion. Dr Catherine Cornu, who coordinates the project along with her colleagues at Université Claude Bernard at Lyon in France, Dr Patrice Nony and Dr Behrouz Kassai: 'We want to develop a model that will enable us to say: if you have this disease, and this drug aimed at this particular mechanism, then this is the study design for you. Ideally, the model would predict the best study design for any disease, but that may take many more years of research. What we do in this project will be the first steps towards that goal.'

Researchers from several European universities work together within the project. They combine expertise in mathematical models, biostatistics and clinical drug trials with specific knowledge about three rare diseases: severe myoclonic epilepsy in infancy (Dravet Syndrome), cystic fibrosis and lymphoblastic lymphoma. Cornu: 'The paediatricians with specialist knowledge of these rare diseases will contribute to the development of computer models, aimed specifically at the mechanism of action of the drugs we want to research. Many models already have been published, but they may need to be modified for our purposes. The models of drug action will be combined with pharmacological models, showing the concentration of the drug on the place of action. These so-called PK/PD models will also need to be modified, corrected to allow for the specific situation in young children. If the liver is not matured, for example, you have to adjust for that.'

In the initial stages of the project, the researchers will aim for specific clinical targets, such as prevention of pulmonary complications in cystic fibrosis. Cornu: 'To develop our methodology, we need to focus. At first it will be one drug, with one purpose and one endpoint we can connect to our disease model. With all that in place, our group can then make a computer model to design the best clinical trial. We can simulate thousands of clinical trials with different designs and compare results: which design yields the highest

precision with the shortest duration and the lowest number of patients? In these rare diseases, there is no second chance to get it right in reality, so a computer simulation can help you prepare the best possible study and give drug trials the best chance to arrive at conclusions.'