Meet the WMC team: Jiří Létal - Statistician

***Dr Létal - Credentials & Experience**: Dr Létal is a Statistician with more than 30 years' experience in biometrics, including 15 years in clinical trial statistical analyses and 15 years in biometrics research & lecturing. Jiri has worked with Wound Market Consulting for 8 years and at several international CROs and pharmaceutical companies including Novo Nordisk (Denmark), Janssen Pharmaceuticals of JNJ '(Belgium), Grünenthal (Germany) and ADDS/Aixial, ICON/PRA or Navitas Life Sciences in a variety of therapeutic areas.*

1. Is there a problem within your area of expertise/industry that you would like to see addressed?

Many smaller biotech or pharma companies struggle with statistical design due to a lack of experience sufficient to meet the complex aims of their studies. They also find it difficult to develop a statistically justifiable size of sample.

The sample size needs to be large enough to ensure that the study is powered sufficiently to give credibly representative results. The client will have their own ideas and different expectations, yet quite often the results arising from a study where the design has been altered due to budget pressures may not be representative and therefore not accepted by the authorities as generalisable to everyday use. Industry can take more persuading than clinicians, as clients are always balancing or minimising costs against the study design. For the Pharmaceutical industry this isn't so much of a problem due to their typically larger budgets than wound care but generally we need to find the balance between the two.

2. Have there been any recent developments in statistical analysis over the last year?

The tools for design, sample size, methods of calculations are well known. Over the last ten years I have seen that Health Authorities have taken new and resource-intensive methods of study design such as adaptive design into account in their assessment of evidence. This is increasing industry's already high cost of product and therapy development.

There has been an increased focus on mathematical modelling and simulations which allow a better understanding of how the robustness of a study design will have an impact on results, for example through missing data or changes to the parameters of data collected.

Several state of the art statistical modelling tools such as JMP in SAS are mentioned in FDA and EMA guidelines and accepted by these bodies as important tools for study design although their use is not mandatory.

The Bayesian method uses experience in probabilities from similar studies and utilises parameters collected from the study. The data collected allows you to set the parameters for the other stages of the study. The Bayesian method is more commonly used in the early phases of trials. Phase 3 trials have stricter requirements because this is the final phase before the product/therapy is released onto the market and applied to clinical practice. They include data from hundreds and thousands of subjects and the statistical analysis is to confirm and demonstrate a significant effect of a new product/therapy to a high standard of reliability. The processes need to be standardised in order to achieve a high quality of manufacturing, clinical monitoring and data analysis.

As a result, the use of the Bayesian method in phase 3 trials is limited. Most publications consist of trial protocols or re-executions of completed 'standard' clinical trials using the Bayesian adaptive design for comparative purposes. The Bayesian method adds data collected in earlier studies and in the study itself

into the analysis and so potentially decreases the required sample size. However, more research and evidence is required before these methods can be accepted into official guidelines.

The alternative to the standard design of clinical studies is to adopt the Adaptive method, whereby the statistical plan and protocol are adapted to the results during the study. This can be a more attractive method as the standard design does not permit substantial modifications to the Protocol nor the Statistical Analysis Plan (especially of Phase 3 trials). Adaptive design implements some interim amendments, an example of this would mean an interim analysis once 50% of subjects have been enrolled in the study. This interim analysis can affect what happens thereafter; the sample size might be re-designed or re-calculated. In my experience the Adaptive method is being adopted more often, especially when the sponsor is looking to reduce time and costs in an already time consuming verification of efficacy and safety for new products. The advantage of the Adaptive design is that it allows a re-evaluation of the theoretical assumptions and you can adapt the clinical process where required or stop the study. One method is to start with a smaller sample size and then increase this if needed after the interim analysis but this approach requires more resources and time from a methodological point of view.

3. What is the most common mistake often made by industry when collecting and processing clinical data?

Proposals are normally based on the clinical point of view and this impacts the design of the study. Because of this, the study quite often does not meet the objective of what it was set out to prove or disprove. Care and consideration from experts and statisticians should be sought during the initial design phases. I recommend discussing the study design with a statistician as early as possible. Identify how we measure and generate results, can we justify it for a narrow population? Multi-centre trials can be more beneficial in these circumstances. In my experience, many oncology studies do not reflect what the aim of the study was intended to show. In one such instance this resulted in discussions with the FDA who raised questions and concerns that were valid. There had been mistakes in the design process and decisions were made without any input from a statistician. The protocol had been submitted and the FDA required significant changes; and this could have been avoided.

4. Four common criticisms of sample sizes?

a) Not enough information from clinicians.
b) Thorough justification for the sample size is missing.
c) Sample size population needs proper consideration so that it is representative of the target market.
d) Managers are the decision-makers on sample size and base their decisions on balancing the information required against Budgets.

5. What are the most common mistakes or problems with statistical reports?

a) We cannot report anything other than what has been described in the protocol and what data is collected. Sponsors' expectations may therefore not be met.
b) Once the study has finished, we cannot change the protocol, even if it was wrong from the beginning. Such mistakes can be only described and partially minimized in statistical plans.
c) Reporting significant effects from a statistical point of view is not a proof of clinical effects! If the sample size is not justified enough and the statistical power is low, it is only an indication of a possible effect, not more.
d) Relying on unreliable data – without verification of correctness of the source data the results are misleading. In analytics, there is a simple rule: rubbish in, rubbish out.
e) Many analysts and decision makers look at the simple average without segmentation by category and rely on "what occurs most often". The conventional mean average – sum divided by count - is very often misleading.
f) Missing comments of noticeable changes – if an unexpected change or effect has been reported, it has to be provided with an explanation.
g) Conclusions should be clearly described and discussed with respect to the aims of study.