Pre Forum Courses: 19 October 2022

From a successful prior elicitation meeting to a reliable probability of success estimate: QDM principles and practicalities

Marco Costantini, Luca Grassano, Giulia Zigon (GSK Vaccines)

Pharmaceutical companies too frequently base their investment decisions on single study outcomes, often observed in over optimistic early-stage phases of the clinical development. Such a common bad practice is one of the leading factors to failing in pivotal confirmatory studies. Implementation of QDM makes it possible to incorporate existing estimates of uncertainty into a sound and quantitative evaluation of the risk of success/unsuccess for ongoing and future clinical trials.

This course aims at describing the key elements of Quantitative Decision-Making (QDM), by introducing the theoretical framework and providing practical examples through case-studies.
At the end of the course, it will be clear how QDM, where fully acknowledged and formally inserted in the company governance, can increase the chances of obtaining marketing authorization for drugs and therapies under development while reducing wrong decisions of investment on candidates with low probability of success.

Time	
9.45 – 10.00	**Welcome and Introduction**
10.00 – 10.30	Introduction to the QDM principles
10.30 – 11.00	From QDM to Probability of Success (PoS)
11.00 – 11.30	Bayesian statistics in the QDM framework
11.30 – 12.00	**Coffee break**
12.00 – 13.00	The role of prior distributions – Metanalysis, expert opinions and elicitation meeting
13.00 – 14.00	**Lunch**
14.00 – 14.30	Q&A
14.30 – 15.00	QDM set up
15.00 – 15.30	PoS calculation
15.30 – 16.00	**Coffee break**
16.00 – 16.30	Practice exercises with R
16.30 – 17:00	Q&A

Validation in Statistical Programming: Way of Working QC and Applied Exercises

Stefano Lombardi, Federico Baratin (GSK Vaccines)

Time	
9.00 – 9.15	**Welcome and Introduction**
9.15 – 9.45	ADSL and related TFL validation - presentation
9.45 – 10.15	ADSL validation -demo (SAS or R)
10.15 – 10.45	**Coffee break**
10.45 – 11.15	DM TFL validation – demo (R or SAS)
11.15 – 12.30	Practical session with exercises
12.30 – 14.00	**Lunch**
14.00 – 14.30	ADAE and related TFL validation – presentation
14.30 – 15.00	ADAE validation – demo (R or SAS)
15.00 – 15.15	**Coffee break**
15.15 – 15.45	AE TFL validation – demo (SAS or R)
15.45 – 16.30	Practical session with exercises
16.30 – 17:00	SAS vs R tips and tricks (on QC programs)
17.00 – 17:15	**Closing**

IBIG Forum: 20-21 October 2022

Day 1: Statistics Beyond Clinical Trials

	Artificial Intelligence and Machine Learning for clinical research	**Chair** Giulia Zigon *(GSK Vaccines)* Veronica Sciannameo *(University of Turin)*
9.45 – 10.00	**Welcome and Introduction**	
10.00 – 10.30	Application of Machine Learning approaches in clinical trials under a personalized medicine prospective	Sara Urru (University of Padua)
10.30 – 11.00	A machine learning perspective on the issue of small sample size: can we overcome the curse of small sample size?	Andrea Ricotti, Piercesare Grimaldi *(University of Turin)*
11.00 – 11.30	BcRAIN: A Deep Learning approach for B-cell repertoire dissection	Alessandro Rossi *(GSK Vaccines)*
11.30 – 12.00	**Coffee break**	
12.00 – 12.30	Machine learning for vaccine candidates' identification	Alessandro Brozzi *(GSK Vaccines)*
12.30 – 13.00	Machine learning in drug development: a case study	Letizia Nidiaci, Federico Agostinis *(Evotec)*
13.00 – 13.15	Q&A	
13.15 – 14.15	**Lunch**	
	Data Quality and Risk Based Monitoring	**Chair** Arturo Lanzarotti *(IBSA)* Fabio Montanaro *(Parexel)*
14.15 – 14.45	Risk-based monitoring in clinical research: past, present and future	Linda Valmorri *(Medineos IQVIA)*
14.45 – 15.15	Risk-based monitoring applied to observational studies: methods and implementation	Lucia Simoni *(Medineos IQVIA)*
15.15 – 15.45	**Coffee break**	
15.45 – 16.30	SAS: From Data Quality to Risk Based Monitoring in clinical trials	Alberto Romanelli *(SAS Institute)*
16.30 – 16.45	Q&A	
16.45 – 17.00	IBIG Annual report	

Artificial Intelligence and Machine Learning for clinical research - ABSTRACTS

Application of Machine Learning approaches in clinical trials under a personalized medicine prospective
Sara Urru (University of Padua)

In the era of big data, the sources and types of data considered are constantly and massively increasing, therefore the need of more powerful and sophisticate techniques has arisen.
Machine Learning (ML) changed the paradigm of traditional programming; while the latter asks for data and rules to return the answers we are looking for, ML returns rules given input and output data. ML techniques are divided into supervised and unsupervised learning. The former refers to regression models and classification problems where the predictors and outcomes are known but the relationship between them is not, while the latter are used for exploratory purposes, to find patterns in the data and cluster items.
In clinical studies they are widely used to identify novel patterns, to predict outcomes and diagnosis and to optimize treatment decisions. Moreover, the aim of ML is to build prediction models reaching the maximal accuracy making them suitable for personalized medicine applications.
Randomized Clinical Trials (RCTs) are the gold standard to estimate the potential causal relationship between treatment and outcome, but, under a personalized medicine perspective, the average treatment effect results to be an unsuited statistics in order to take into account the heterogeneity among patients based on genetic, environmental, and lifestyle factors.
A case-study on type 2 diabetes is reported to show the power of an ensemble of ML predictive model in the framework of precision medicine. ML is fundamental to help us see beyond our limits, but it is not sufficient on its own; clinicians, statistician and computer scientists are needed to guide and interpret ML models.

A machine learning perspective on the issue of small sample size: can we overcome the curse of small sample size?
Andrea Ricotti, Piercesare Grimaldi (University of Turin)

It is well known that machine learning (ML) usually requires large sample sizes, however small sample sizes being common in clinical studies, and the fact that limited data is problematic, only a limited number of papers have systematically investigated how the ML validation process should be designed to help avoid optimistic performance estimates.
The three most common difficulties while managing small datasets are unbalanced data, high/low dimensionality, and high bias/prediction variance.
Data unbalance occurs when one or more categories are underrepresented. This is a problem while training and validating. During training, the learner only sees a small number of cases in sparse categories, limiting its ability to generalize. To partially overcome this issue, few algorithms such as RUSboost and SMOTHEBoost have been developed.
High dimensionality, the number of covariates is larger than the number of cases, produces model overfitting so it cannot be generalized to a new dataset. Cross validation is a method to evaluate ML models by training several ML models and correcting for overfitting in order to improve the ability to generalize. Standard k-fold cross-validation is not optimal for small datasets, and more appropriate approaches such as nested cross-validation should be applied.
In this seminar we will expose the limits and issues associated with use of ML on small sample sizes showing case study examples in clinical data, with particular focus on neuroscience.

BcRAIN: A Deep Learning approach for B-cell repertoire dissection
Alessandro Rossi (GSK Vaccines)

Immune system guarantees protection against disease and pathogens by a highly diverse adaptive response that mutates the B-cell receptor (BCR) to produce neutralizing antibodies (Ab) and develop Memory B-cells to prevent future infections. Shedding light on this process is fundamental in Vaccines development, but the characterization of long-lasting protective Memory B-cell is usually compared with capturing the needle in a haystack. We showed that AI can provide the representational power to tackle this task by training a Deep Learning model on a 52.3M sequences dataset to embed them in a single digital signature together with physicochemical properties. Results shows a coherent description when tested on a validation set of 11.9M of sequences. This provided us a way to build "virtual placebos" from sequencing data of healthy subjects, representing a baseline for immune state. This information will reduce the need of collecting clinical samples. Contrasting virtual placebos against data from vaccinees or infected subjects enables the description of specific BCR populations induced by pathogen exposure. All together these innovative approaches can help in understanding the rules governing the immune response and hence accelerating pre-clinical and clinical development processes.

Machine learning for vaccine candidates' identification
Alessandro Brozzi (GSK Vaccines)

Most likely you all know that commercial vaccines against virus SARS-CoV-2 are formulated with a single viral protein called Spike(S) that the virus expresses on its cell surface. Once administered intramuscularly, it is safe, and it confers effective immunity against the severe disease caused by the whole living virus. But not all the proteins of a pathogen would work immunologically the same as Spike(S). Identifying the proteins (called antigens) that confer protective immunity out of the full repertoire of proteins a pathogen is constituted, is crucial to successful vaccine development. If SARS-CoV-2 virus encodes totally only 29 proteins, a bacterium has on average 2000 proteins, making the antigen prediction for bacteria "a needle in the haystack". We proved that the task of predicting good antigens can be machine-learnable. We tested performances on ten different bacterial species independently, finding an average accuracy measured by Area Under the Curve of 0.857. We show empirically that applying machine learning to vaccine candidate identification the number of in-vivo animal tests needed to identify a fixed number of antigens can be reduced by 45% on average with respect to traditional methods.

Machine learning in drug development: a case study
Letizia Nidiaci, Federico Agostinis (Evotec)

The huge increase of available data in Drug discovery and Clinical Drug Development, and the development of new machine learning methodologies have made it possible to extract information that are useful both scientifically and for decision support. This can lead to faster drug development while limiting the likelihood of a study being stopped at a late stage. The goal of the presentation is to provide an overview of some machine learning techniques and show their application in different areas of drug development. Finally, one model is presented, it can be applied in the translational phase to predict the probability of failure of a clinical trial. The model uses information contained in the protocol, information obtained from previous trial phases, and molecule-specific information to predict the outcome of the study.

Data Quality and Risk Based Monitoring - ABSTRACTS

Risk-based monitoring in clinical research: past, present and future
Linda Valmorri (Medineos IQVIA)

The concept of Risk-Based Monitoring (RBM) in clinical trials will be introduced by the definition of the industrial strategy of Risk-Based Performance Management (RBPM), focusing on the stakeholders and tools of this systematic process. An overview on the international RBM implementation will be provided, highlighting the impact of the Covid-19 pandemic on clinical trials management and monitoring methods. For the future, an increasingly integrated approach between the trial management oriented to deliverable strategic objectives and risk optimization will be recommended.

Risk-based monitoring applied to observational studies: methods and implementation
Lucia Simoni (Medineos IQVIA)

The Risk-Based Monitoring approach will be placed in the context of the observational studies management. The operational tools able to ensure the trial objectives achievement maintaining an acceptable level of risk will be described, by commenting the application and implementation of Transcelerate checklist too. Finally, the need to adapt these tools to the peculiar characteristics of each trial will be underlined: it is essential to use appropriate and "study-specific" performance indicators to monitor and evaluate the correct management of the trial during all its phases.

SAS: From Data Quality to Risk Based Monitoring in clinical trials
Alberto Romanelli (SAS Institute)

In modern clinical trials it is no longer sufficient to monitor risks through an individual productivity tool like excel. From the data and its quality to the people involved in the processes it is necessary to set up a platform able to identify, map, assess and mitigate the risks in a comprehensive way.

Day 2: Statistics in Clinical Trials

	Interim Analysis: Methods & applications	**Chair** Angela Gambioli *(UniMIB)* Marco Costantini *(GSK Vaccines)*
9.15 – 9.30	**Welcome and Introduction**	
9.30 – 10.00	Group Sequential Designs: General framework, methods and applications with pros & cons	Giulia Lorenzoni *(University of Padua)*
10.00 – 10.30	Interim monitoring: repeated significance tests and stochastic curtailment	
10.30 – 10.45	Q&A	
10.45 – 11.00	**Coffee break**	
11.00 – 11.30	On the distribution of the power function induced by a design prior	Fulvio De Santis, Stefania Gubbiotti *(University of Rome "La Sapienza")*
11.30 – 12.15	Interim analysis: case studies from Chiesi experience	Stefano Vezzoli *(Chiesi Farmaceutici)*
12.15 – 12.35	The health authorities' perspective	Giulia Zigon *(GSK Vaccines)*
12.35 – 12.50	Q&A	
12.50 – 13.40	**Lunch**	
	Estimands & Estimation	**Chair** Daniele Bottigliengo *(GSK Vaccines)* Andrea Nizzardo *(Evotec)*
13.40 – 14.20	The Estimand Journey: Opportunities and Challenges	Khadija Rantell *(MHRA)*
14.20 – 15.00	Estimation of treatment effects in short-term depression studies. An evaluation based on the ICH E9(R1) estimands framework	Marian Mitroiu *(Biogen International GmbH)*
15.00 – 15.40	Treatment policy estimands for recurrent event data with missing data: COPD vaccine case study using IPCW	Martina Amongero *(University of Turin)*
15.40 – 16.20	Estimands based on composite strategy: examples and regulatory perspectives	Khadija Rantell *(MHRA)*
16.20 – 16.30	Closing	

Interim Analysis: Methods & applications - ABSTRACTS

Group Sequential Designs: general framework, methods and applications with pros & cons
Giulia Lorenzoni (University of Padua)

Group Sequential Designs (GSDs) incorporate the sequential evaluation of data collected through the trial at prespecified intervals. This is known as interim monitoring, which has become a central part of modern clinical trials. It consists of repeatedly analyzing efficacy and safety information as data comes in, offering the possibility to stop the study at the interim looks for efficacy or futility before the planned final analysis. Compared to fixed designs that analyze data only once at the end of the trial, GSDs provide greater flexibility and are more efficient. However, their design and conduction could be challenging. The presentation aims to provide general concepts regarding GSDs and discuss the pros & cons of GSDs use in clinical research.

Interim monitoring: repeated significance tests and stochastic curtailment
Giulia Lorenzoni (University of Padua)

Interim monitoring translates to testing a statistic summarizing the difference in the primary endpoint among treatment groups, i.e., the null hypothesis is tested at each interim analysis. Testing repeatedly the null hypothesis as data comes in without correcting the alpha level results in the inflation of the Type I error rate, i.e., increased false discovery rate. Several approaches are available to control the false discovery rate. Choosing the most appropriate one is a critical component of the interim monitoring planning, together with selecting an adequate stopping rule to be applied to the interim analysis. The presentation will discuss the available methodologies to control the false discovery rate and methods for interim monitoring decisions based on stochastic curtailment.

On the distribution of the power function induced by a design prior
Fulvio De Santis, Stefania Gubbiotti, Francesco Mariani (University of Rome "La Sapienza")

The power function of a test - the probability of rejecting the null hypothesis on a parameter - is routinely used in drug development to quantify the chances of success of a clinical trial.
The standard use of this function is to evaluate it at a specific value of the parameter (minimal clinically relevant effect) and to design the experiment accordingly. Instead of fixing a specific design value for the parameter, the Bayesian predictive power considers the expected value of the standard power function with respect to a distribution assigned to the parameter under test (design prior). This quantity is often proposed in the literature as an alternative to the usual power function since it takes into account possible uncertainty on the true value of the parameter assumed for trial design. However, looking only at the expected value of the whole probability distribution induced by the design prior on the power might be reductive and misleading.
In this communication we study this probability distribution for some specific models that are relevant in clinical trials. The study sheds light on the relationships between the degree of information in the data and in the design prior that have to be respected in order to construct a successful experiment.

Interim analysis: case studies from Chiesi experience
Stefano Vezzoli (Chiesi Farmaceutici)

Case studies from Chiesi experience where interim analyses improved the efficiency of trial design will be presented and some subtleties associated to their practical implementation will be discussed. Examples from 3 studies will be described. (1) Interim analysis allowing for an early stop for efficacy. (2) Interim analysis for futility assessment based on conditional power, with count data analysed using a negative binomial model. (3) Interim analysis for dropping placebo in a three-arm "gold standard" non-inferiority design, with hierarchical testing of multiple endpoints.

The health authorities' perspective
Giulia Zigon (GSK Vaccines)
What is the regulatory perspective to consider when deciding to implement an adaptive trial? The "Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry" describes principles, types, methods, and considerations on the topic. The key elements of the guidance will be pr esented along with a case study where, for a group sequential trial, FDA requested to modify the boundaries for the interim analysis.
Adaptive Designs for Clinical Trials of Drugs and Biologics (fda.gov)

Estimands & Estimation - ABSTRACTS

The Estimand Journey: Opportunities and Challenges
Khadija Rantell (MHRA)

The ICH E9(R1) addendum on Estimands and Sensitivity Analyses in Clinical Trials has introduced a new estimand framework for the design, conduct, analysis, and interpretation of clinical trials. Notably, the addendum introduced the concept of intercurrent events and different possible strategies to address these. Intercurrent events may impact the assessment and subsequent interpretation of the outcome of interest. Opportunities and challenges (e.g. incorporating estimands in protocols) will be covered in the first part of this talk. Examples of proposals for handling intercurrent events (e.g. composite strategy) and regulatory perspectives on these will be presented in the second part of this talk.

Estimation of treatment effects in short-term depression studies. An evaluation based on the ICH E9(R1) estimands framework
Marian Mitroiu (Biogen International GmbH)

We re-analysed six clinical trials evaluating a new anti-depression treatment using common analysis methods and a principal stratum analysis. We translated each analysis into the implicitly targeted estimand, and formulated corresponding clinical questions. We could map six estimands to the analysis methods. The same analysis method could be mapped to more than one estimand. The fact that an analysis could estimate different estimands emphasizes the importance of prospectively defining the estimands targeting the primary objective of a trial. The fact that an estimand can be targeted by different analyses emphasizes the importance of prespecifying precisely the estimator for the targeted estimand.

Treatment policy estimands for recurrent event data with missing data: COPD vaccine case study using IPCW
Martina Amongero (University of Turin)

Under the Treatment Policy, whether an intercurrent event has occurred or not is irrelevant, the data will be collected and analyzed regardless. Within this framework, we explore an approach called Inverse Probability of Censoring Weighting (IPCW) to deal with missing data. As a motivating example we consider a Phase 2 COPD Vaccine study.

Estimands based on composite strategy: examples and regulatory perspectives
Khadija Rantell (MHRA)

The ICH E9(R1) addendum on Estimands and Sensitivity Analyses in Clinical Trials has introduced a new estimand framework for the design, conduct, analysis, and interpretation of clinical trials. Notably, the addendum introduced the concept of intercurrent events and different possible strategies to address these. Intercurrent events may impact the assessment and subsequent interpretation of the outcome of interest. Opportunities and challenges (e.g. incorporating estimands in protocols) will be covered in the first part of this talk. Examples of proposals for handling intercurrent events (e.g. composite strategy) and regulatory perspectives on these will be presented in the second part of this talk.