IBIG Forum 2020 Abstracts

2 OCT 2020: QUANTITATIVE DECISION MAKING (QDM) IN THE CLINICAL DRUG DEVELOPMENT

Chair: Marco Costantini, Lead Statistician, GSK Vaccines

Quantitative decision-making: rationale, frameworks and probabilities of success

Gaëlle Saint-Hilary, Statistical Methodologist, Servier and Politecnico di Torino

Quantitative decision-making (QDM) in pharmaceutical development aims at making an optimal choice between several alternatives, at multiple time points during a drug life cycle, based on the current knowledge of the investigational product. For example, go/no-go decisions are made at the end of phase 2 clinical trials, according to the evidence from the accumulated data. Decisions are not limited to the continuation or the termination of the development but are also needed to choose the targeted indication, the patient population, the doses, or the study designs. The pre-specification of QDM frameworks with objective criteria is a driver for better decision-making. In confirmatory studies, the decisions are typically made based on a 'significant p-value', but decision criteria using the size of the treatment effect are also increasingly used, since they are sensible to account for the clinical relevance of the results. Within these frameworks, the calculation of probabilities of success permit to assess the confidence level that the objectives are met, taking into account available and future evidence and uncertainties. Understanding the framework's operating characteristics helps optimizing the study design or the drug development plan, and they facilitate cross-functional communication and planning. An effective communication makes decision-makers understand how strategic quantitative thinking supports better decisions, by increasing awareness of the risks in the presence of uncertainty, and by quantifying and controlling the risk of false decisions.

A GSK-developed R Shiny app as an interactive tool for QDM

Luca Grassano, Expert Statistician GSK Vaccines

Shiny is a powerful R package that allows proficient R programmers to develop and deploy interactive analytical applications to a broader audience.The strength of the Shiny apps rely on the ability to adapt to the end users' preferences in no time, providing the desired outputs with only few clicks. At GSK Vaccines, a Shiny app was developed to facilitate the QDM exercise within the larger clinical community when exploring alternative options for any program development. A demo of the QDM Shiny app will be given to complement the general framework.

A novel measure of drug benefit–risk assessment based on Scale Loss Score (SLoS)

Pavel Mozgunov, Lecturer in Medical Statistics, Lancaster University

Quantitative methods have been proposed to assess and compare the benefit-risk balance of treatments. Among them, multicriteria decision analysis (MCDA) is a popular decision tool as it permits to summarise the benefits and the risks of a drug in a single utility score, accounting for the preferences of the decision-makers. However, the utility score is often derived using a linear model which might lead to counter-intuitive conclusions; for example, drugs with no benefit or extreme risk could be recommended. Moreover, it assumes that the relative importance of benefits against risks is constant for all levels of benefit or risk, which might not hold for all drugs. In this presentation, we will present Scale Loss Score (SLoS) as a new tool for the benefit–risk assessment, which offers the same advantages as the linear MCDA utility score but has, in addition, desirable properties permitting to avoid recommendations of non-effective or extremely unsafe treatments, and to tolerate larger increases in risk for a given increase in benefit when the amount of benefit is small than when it is high. We will demonstrate the properties of the proposed tool compared to the conventional linear MCDA in a comprehensive simulation study.

Assurance in vaccine efficacy clinical trial design based on immunological responses

Andrea Callegaro, Lead Statistician GSK Vaccines

The concept of assurance is defined as the unconditional probability that a clinical study will yield a positive outcome. This usually implies that a statistically significant result is obtained at the end of the study in question, according to a standard frequentist significance test. Assurance may be seen as the expectation of the power, averaged over the prior distribution for the true unknown vaccine effect. In this work, we examine assurance in the specific context of vaccine development, where the prior information is determined from an immunological Phase 2 study, while the outcome of the Phase 3 study represents a clinical endpoint.

9 OCTOBER 2020: SAS, R, PYTHON – DIFFERENCES, SIMILARITIES AND POTENTIALITIES OF WIDELY USED STATS SOFTWARE

Chairs: Angela Gambioli, Statistical Analyst GSK Vaccines
Veronica Sciannameo, PhD Student, University of Padua

Using R for Reporting and Analyzing Clinical Trial Data

Daniele Bottigliengo, PhD Student, University of Padua

The analysis and the report of clinical trial data is a crucial task of a biostatistician's work to ensure that the results are effectively communicated to clinicians and stakeholders. From the analysis side, "state-of-art" statistical methods, which heavily rely on simulations and require high computing performances, are increasingly being used to analyzed clinical trial data. In light of this, the importance of building instruments that effectively report and communicate the results of advanced statistical models is more and more being highlighted, with a particular focus on interactive and intuitive tables and graphs. R and R studio IDE are valuable instruments to accomplish both tasks throughout robust workflows. The presentation aims to discuss the use of R in clinical trial environments, showing some tools that allow for a standardized and robust implementation of analyses and reports of clinical trial data.

Learn, Prototype and Deploy with Ease: A Case for Python in Research

Arjun Magge, Research Scientist, University of Pennsylvania

Python has emerged as a popular choice of programming language in data science for its ease of use and rapid development capabilities. The large collection of libraries developed by academic and industrial community members, especially in the area of machine learning and deep learning, has enabled the research community to develop informatics solutions across numeric, text, images, audio, and video data formats. Python also provides the essential libraries for model development, data analysis and visualization across execution interfaces, making it an ideal tool for education. In this presentation, I will discuss and demonstrate GeoBoost2, an application that uses natural language processing (NLP) to normalize virus nucleotide sequence metadata. We used deep learning and machine learning frameworks in Python to create, train and deploy information extraction models to support virus phylogeography research. This presentation attempts to make the case for adopting Python as a primary programming language for the teacher, student, researcher and application developer in everyone.

A population-based statistical analysis using SAS-EG: The case of COVID-19 in Friuli Venezia Giulia

Michele Gobbato, Statistician, ARCS Friuli Venezia Giulia

The aim of the presentation is to show a use of SAS-Enterprise Guide, with applications of management and statistical analysis of health-related data, focusing on methodology and software's tools. The epidemiological data-warehouse of Friuli Venezia Giulia (FVG) covers the entire population of the region (1,200,000 persons) and contains information extracted by different administrative database, linked at individual level. SAS-EG is the software used to deal and analyse all these big data. During the COVID-19 pandemic a database of patients positive for SARS-COV2 test, residing in FVG, was created and daily updated through SAS-EG. Demographical and clinical variables such as sex, age, patient's comorbidities, vaccinations, Angiotensive II Reception Blockers (ARBs)/Sartan's prescriptions and geographical residence were collected. Descriptive analyses and statistical logit models were performed to study the determinants of a highly probability of hospitalization.

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16 October 2020: Clinical Trial Management during the COVID-19 Pandemic – Guidelines & Practical Impacts

Chair: Giulia Zigon, Lead Statistician, GSK Vaccines

Clinical Monitoring during Covid Time: What we learnt to anticipate the Future

Roberto Vallalta, Clinical Operations Pharma Manager, GSK

COVID time changed the ways of living and also the ways of monitoring. During the worst month of the pandemic in Italy the emergency has pushed for change Pharma Companies and Health Authority in order to deliver clinical trials, to grant quality of our data and to maintain our patients' rights and safety. During the presentation we will discuss some of these actions trying to understand how these actions has helped us to anticipate the future of our business.

The Impact of COVID-19 on Estimands and Estimation

Thomas Drury, Statistics Leader, GSK

The COVID-19 global pandemic and the restrictive social distancing measures to combat it has affected everyone. Clinical trials have been impacted through site closures, staff shortages and travel restrictions in addition to patients with COVID-19 or risk factors forcing them to shield from the virus. These changes to the standard clinical setting has created more potential for intercurrent events such as treatment interruptions, permanent discontinuations, or even death. The pandemic may have also increased missed assessments or study withdrawals, increasing missing data. How to deal with these issues to mitigate their impact on ongoing studies was matter of serious concern. The information and ideas presented are based on the work of the Estimands special interest group at GlaxoSmithKline which became formalized for internal guidance.

Impact of Covid-19 on Assessment of Safety in Clinical Trials

Jennifer Shannon, Statistics Director, GSK

Many ongoing clinical trials will be impacted by COVID-19. One important aspect of clinical trials potentially impacted is the evaluation of safety. Teams should consider these 3 areas of focus :

- Characterizing the incidence of COVID-19 infection and important characteristics of subjects diagnosed with COVID-19 during the trial
- Describing safety outcomes within the COVID-19 infected subpopulation
- Assessing the impact of COVID-19 related clinical trial operational and logistical difficulties on the interpretation of safety data for all subjects

Suggested analyses will provide a structure to describe the data in a consistent manner that will allow for potential conclusions as to whether the COVID-19 pandemic measurably impacted the trial and the impact to safety outcomes specifically. These analyses also facilitate the evaluation of whether differences in COVID-19 related safety could differ between treatment arms within a study and between subjects with COVID-19 infection versus those without.

Mapping COVID-19 related data into SDTM

Stefania Mirandola, Data Manager, Chiesi Farmaceutici

Purpose of the presentation is to provide a summary of Chiesi DM/STAT analysis of COVID-19 regulatory guidance and CDISC guidelines on data collection and SDTM for ongoing studies: this will be a journey starting from regulatory position to Chiesi actions on clinical trials, focusing in particular on CRF data collection, SDTM preparation and impact on data management documents.

23 OCTOBER 2020: TAXONOMY OF SUBGROUP-RELATED ANALYSES AND ISSUES IN CLINICAL TRIALS

Chair: Fabio Montanaro, Head of Statistics and Data Management, Latis

Taxonomy of exploratory subgroup-related analyses in clinical trials Part 1: Pre-specified analysis

David Svensson, Senior Statistical Science Director, AstraZeneca

In this talk, we will overview typical inherent difficulties arising when assessing pre-specified subgroups for exploratory purposes and look at a range of novel methods that have been suggested in the literature for facilitating this. The setting we discuss range from regulatory Consistency Assessment (e.g., regional) to Selection of a subgroup from a fixed candidate set. Typical difficulties center around quantitative assessment of likelihood of chance-findings, and bias reduction of estimates in a winning (selected) subgroup. We will overview a range of proposed approaches, ranging from Bayesian shrinkage, BIC model averaging and some resampling ideas; we also will discuss some novel ideas around subgroup visualizations (e.g., the UpSet graph). All of the above reflect the scope and current work of the EFSPI Subgroup SIG working group. Note that the focus will be mainly be on computational aspects and the corresponding inherent pros and cons; there will be less on regulatory view and guidelines. Also, formal multiple testing is outside scope of this talk.

Taxonomy of exploratory subgroup-related analyses in clinical trials Part 2: Data-driven ML analysis

David Svensson, Senior Statistical Science Director, AstraZeneca
A joint work with Ilya Lipkovich

In this part 2, we look at exploratory data-driven subgroup detection and Individual Treatment Effects (ITE), an area where Machine Learning (ML) is central. We argue why such methods are generally strong for finding interactions, and we overview the recent developments in this area. We discuss an important distinction between general purpose ML and ML for randomized clinical trials (the latter with its causal inference flavor and potential issues with prognostic variables). Many methods have been proposed and range from tree-based to penalized regression methods. We will focus on the former and give a basic general introduction to trees (CART), and then overview tweaked versions for RCTs such as Virtual Twin, IT, MOB, GUIDE, STIMA, SIDES, and ensemble-based methods (e.g., Causal Forest). A key aspect discusses is the paradigm of considering subgroup detection as a special case of model selection. We shortly also discuss RCTs with more than two treatment arm (where the overall literature so far has focused mostly) and show some recent ideas for dose-response trials. The above also reflects ongoing work and interest of the EFSPI Subgroup SIG working group.

All the things I wish I had known before I tried to detect a subgroup

Nicole Krämer, Senior Manager Principal Biostatistician, MorphoSys AG

With growing interest in personalized medicine, subgroup analyses (with various degrees of pre-specification) arise at different stages of clinical drug development. Despite existing guidance documents on confirmatory ad exploratory subgroup analysis, statisticians working in this field may encounter difficulties in setting up, analyzing or interpreting subgroup analyses. Further, recent years have seen an increase in completely data-driven methods using advanced analytical methods. While these methods can be powerful, they also add additional pitfalls and challenges. In our talk, we will discuss some of the common errors in application and interpretation of subgroup identification & analysis methods.

An introduction to Optimizing Treatment for a given patient: ITR analysis

Paolo Eusebi, Biostatistician, UCB

Personalized medicine is a field that is receiving a lot of attention both in terms of real-world applications and development of methodology. Subgroup analysis procedures developed for personalized medicine applications are commonly based on data-driven approaches. These procedures are usually conceptualized within two main frameworks: identifying the right patient for a given treatment or identifying the right treatment for a patient.
In this talk, a review of methods that fall within the latter framework is reviewed, i.e. the so called ITR (individual treatment rule) or OTR (optimal treatment regime).
The presentation will review the basics of the methodology, with emphasis on multiple treatments and Outcome Weighted Learning approaches. A comprehensive list of available software options will be also showcased. Simulation results will be presented and discussed.

30 OCTOBER 2020: DATA VISUALIZATION FOR A BETTER COMMUNICATION WITH NON-STATS PEOPLE

Chairs: Luca Grassano, Expert Statistician, GSK Vaccines
Andrea Nizzardo, Biostatistical Science Manager, Menarini Ricerche

Clinical Data Reporting: from standard Tables, Listings and Figures to advanced and interactive Data Visualization

Nicola Celli, CEO, Blue BI
Anna Proserpi, Consultant, Blue BI
Alberto Romanelli, SAS Domain Expert Commercial, SAS

The ability to leverage the power of data and analytics has started to play an increasingly central role in clinical research. Therefore, nowadays using data in decision-making has become an important focus for financial sustainability in the pharmaceutical sector. During this webinar, through the use of Sas Visual Analytics, we will show how power of data visualization is able to discover evidence and insights through the data and how it can be used to monitor the different phases of a study in order to optimize the management.

A SAS graphical macro interface for descriptive tables in clinical trials

Davide Soranna, Biostatistician, Istituto Auxologico Italiano

After the completion of a clinical study, descriptive tables are usually prepared by the researchers to report the main results in scientific papers. These tables take a long time to be ready, especially if the researcher does not know any programming languages. An automatic solution allowing inexperienced programming users (e.g. physicians) to produce descriptive tables would be, then, very useful.
The biostatistical group of Istituto Auxologico Italiano and the University of Milano-Bicocca have implemented, in SAS Macro language, an automatic graphical interface to simplify the creation of descriptive tables. The program is mainly based on the %WINDOW macro statement, and it is divided into three parts:

1) data input (in .sas7bdat format) and selection of variables of interest
2) categorization of continuous variables (if needed) and renaming/changes of qualitative variables levels
3) implementation of normality tests and stratified analysis (if necessary).

The output table is in .rtf format with the template commonly used in scientific clinical papers.

Innovative graphical solutions to explore and visualize clinical trial data with R Shiny

Valentino Conti, Expert Biostatistician, GSK Vaccines Institute for Global Health

Statisticians working on Phase I and II studies often received requests for unplanned or exploratory analysis. An early data visualization and exploration by clinicians and statisticians can support better planning of exploratory analysis. A R Shiny visualization app can fit most laboratory data from vaccine trials, taking advantage of the common SDTM data structure, to promptly respond to the study team's questions.

An interactive platform to aggregate and display data from multiple sources

Grace Hsu, Senior Biostats Consultant, Cytel

Dashboards are not a new concept by any stretch, and this presentation will illustrate how an interactive platform was designed and developed for the purpose of efficiently disseminating knowledge regarding clinical trials for the COVID-19 pandemic. Emphasis will be placed on practical challenges and solutions to setting up trial trackers based on lessons learned with the global COVID-19 Trial Tracker (https://www.covid19-trials.com). Though the development of the dashboard itself was done completely in R, multiple team members with key skillsets were needed and will be reviewed, as well as the process required for transitioning to a more robust platform. Beyond the specific example of the COVID-19 trial tracker that will frame and drive this presentation, there will be brief discussion regarding the functionality of this platform in other research contexts and frameworks where the goal is to provide regular monitoring and access by cross functional teams to a dynamic body of data.