IBIG Forum: Milano, 9-11 ottobre 2023 (Bayer)

Increasing success rate in drug development:

The growing importance of statistics and statisticians

9th October 2023 - Pre-forum Course (9.00 – 17.00)

A pragmatic approach to multiple endpoints resolution: Stefano Vezzoli (Chiesi) e Luca Grassano (GSK)

Multiplicity is a crucial aspect in clinical trial design and analysis. This course will present the general multiplicity issue and how this impacts the interpretation of trial results. Several multiplicity adjustment methods will be described, ranging from simpler parametric approaches to non-parametric graphical procedures. A perspective on the methods will be provided in terms of operating characteristics and implementation in the analysis. In the practical session, case studies will offer the possibility to become familiar with the software implementation (e.g., R, Mediana package or SAS) and to evaluate multiplicity adjustment options during the design phase of clinical trials.

10th October 2023 - Forum

9.00 – 9.45	**Registration**	
9.45 – 10.00	**Welcome & Introduction**	IBIG Steering Committee
The rise of digital superpowers: new perspectives on artificial intelligence and machine learning in drug development		**Veronica Sciannameo Luca Grassano**
10.00 – 10.30	**Topic introduction: ML in clinical research**	Andrea Ricotti
10.30 – 11.00	**Estimating individual treatment effects on COPD exacerbations by causal ML on RCTs**	Kenneth Verstraete
11.00 – 11.30	**Coffee Break**	
11.30 – 12.00	**Fuzzy sets in probability trees: a novel interpretable AI decision making model**	Giulia Capitoli
12.00 – 12.30	**A novel method for the classification of entire genomes of Neisseria meningitidis with a bag-of-words approach and ML**	Margherita Bodini
12.30 – 13.00	**Beyond Z Factor: new methodologies to distill high throughput Screening data**	Luca Vedovelli
13.00 – 14.00	**Lunch Break**	
Historical data in support of drug approval: opportunities and challenges		**Marco Costantini Stefano Vezzoli**
14.00 – 14.30	**Beyond the classical type I error: Bayesian metrics for Bayesian designs using informative priors**	Gaelle Saint-Hilary
14.30 – 15.00	**Bayesian dynamic borrowing approach for a meningitis B vaccine label update indicating its effectiveness against infections caused by Neisseria Gonorrhoeae**	Elisa Cinconze
15.00 – 15.30	**External information borrowing in hypothesis testing under potential heterogeneity**	Silvia Calderazzo
15.30 – 16.00	**Coffee Break**	
16.00 – 16.30	**Bayesian model-informed analysis to estimate maintenance of efficacy**	Guillemette de La Borderie
16.30 – 17.00	**Navigating challenges in RCT conduct: A novel Bayesian adaptive semiparametric approach handling primary and secondary endpoints in pediatric trial design**	Danila Azzolina

The rise of digital superpowers: new perspectives on artificial intelligence and machine learning in drug development

The success rate of new drug development is notoriously low, yet the potential financial rewards are enormous. Many strategies have been used by pharmaceutical companies to attempt to increase the success rate of drug development, but this goal is still difficult to achieve in many situations. The emergence of Artificial Intelligence (AI) and Machine Learning (ML), however, has opened up new possibilities for improving decision-making throughout the development path of pharmaceutical products, from very early discovery phases to clinical trials. Thanks to the exponential growth in biomedical data in recent years, these automated tools can identify patterns and extract useful information at scale. With the ability to accelerate the search for chemical or biological entities with desirable functional activity, AI & ML technologies could revolutionize drug discovery. In this session, we will discuss some case-studies to explore the future potential and the limitations of AI and ML in drug development.

Topic introduction: Machine Learning in clinical research

Andrea Ricotti, Clinical Trial Unit AO Ordine Mauriziano, Turin

Precision medicine is a different approach to clinical research and patient care that focuses on treating disease by integrating multi-data-sources from an individual to make patient-tailored decisions. That implies using large and complex datasets, novel models to process and understand this complexity. At the same time, computer science has progressed rapidly to develop techniques that enable the storage, processing, and analysis of these complex datasets. Machine learning is a branch of artificial intelligence that aims to identify complex patterns in data. Machine learning allows for broad analysis of large datasets and ultimately a greater understanding of human health and disease in order to provide clinically useful tools for individual treatment decisions or to classify strains and identify genes considered relevant or to develop new methodologies to distill High Throughput Screening Data or to identify new predictors associated with risk factors.

Estimating individual treatment effects on COPD exacerbations by causal machine learning on randomized controlled trials

Kenneth Verstraete, PhD Researcher at Katholieke Universiteit Leuven

This study aimed to develop machine learning models to estimate the individual treatment effects (ITE) of interventions using data from randomized controlled trials. We used data from two trials, SUMMIT (NCT01313676) and IMPACT (NCT02164513), focusing on the annual COPD exacerbation rates. We developed a novel metric called the Q-score to assess the power of causal inference models. The results showed that the ML model, specifically the Causal Forest, successfully estimated the ITE in both trials, with the quantiles of patients exhibiting the strongest ITE experiencing the largest reductions in exacerbation rates. These findings demonstrate the potential of ML models for individual treatment decisions in COPD, providing clinically useful tools. Article: https://doi.org/10.1136/thorax-2022-219382

Fuzzy sets in probability trees: a novel interpretable AI decision making model

Giulia Capitoli, School of Medicine and Surgery, University of Milano-Bicocca

The need for fully human-understandable models is increasingly being recognised as a central theme in AI research. The acceptance of AI models to assist in decision making in sensitive domains will grow when these models are interpretable, and this trend towards interpretable models will be amplified by upcoming

regulations. One of the killer applications of interpretable AI is medical practice, which can benefit from accurate decision support methodologies that inherently generate trust. In this work, we propose FPT, (MedFP), a novel method that combines probabilistic trees and fuzzy logic to assist clinical practice. This approach is fully interpretable as it allows clinicians to generate, control and verify the entire diagnosis procedure; one of the methodology's strengths is the capability to decrease the frequency of misdiagnoses by providing an estimate of uncertainties and counterfactuals. Our approach is applied as a proof-of-concept to two real medical scenarios: classifying malignant thyroid nodules and predicting the risk of progression in chronic kidney disease patients. Our results show that probabilistic fuzzy decision trees can provide interpretable support to clinicians, furthermore, introducing fuzzy variables into the probabilistic model brings significant nuances that are lost when using the crisp thresholds set by traditional probabilistic decision trees. We show that FPT and its predictions can assist clinical practice in an intuitive manner, with the use of a user-friendly interface specifically designed for this purpose. Moreover, we discuss the interpretability of the FPT model.

A novel method for the classification of entire genomes of *Neisseria meningitidis* with a bag-of-words approach and machine learning

Margherita Bodini, Senior Data Scientist, GSK

Whole genome sequencing of bacteria has many applications in strain classification for surveillance purposes, that would benefit from the use of machine learning. However, using entire bacterial genomes as input for machine learning algorithms poses difficulties due to the genome sizes, fragmented sequences, and substantial variability between strains which all impede direct comparison of the genomes, without alignment or typing. We have developed a machine learning method that uses entire bacterial genomes to classify strains and identify genes considered relevant by the classifier and applied it to relevant case examples for Neisseria meningitidis.

Beyond Z Factor: New Methodologies to Distill High Throughput Screening Data

Luca Vedovelli, Unit of Biostatistics, Epidemiology and Public Health, University of Padua

In the intricate domain of pharmaceutical research, high-throughput screening (HTS) serves as a formidable tool in the exploration of biochemical, genetic, and pharmacological variables, enabling a swift and comprehensive analysis of vast compound libraries. Traditionally, the Z' factor has been employed as a predominant statistical metric, providing a robust assessment of assay quality and data reproducibility in HTS studies. However, given the accelerating data complexity, it is of utmost importance to reconsider the exclusive reliance on the Z' factor as the primary tool of data interpretation.
This presentation purports to introduce some innovative methodologies that supersede the limitations of the Z' factor, concentrating on the extraction, assimilation, and comprehension of HTS data. The methods, grounded in sophisticated machine learning algorithms, artificial intelligence paradigms, and robust statistical models, are projected to augment the preciseness and efficiency of HTS data interpretation. They are aimed at mitigating false positives and negatives, accentuating hit detection, and unmasking intricate patterns that are imperceptible through traditional statistical approaches.
By espousing these methodologies, it is envisaged that a paradigm shift in the analysis of HTS data can be affected, surpassing the inherent restrictions of traditional statistical parameters and capitalizing on the rich potential of advanced bioinformatics.

Historical data in support of drug approval: opportunities and challenges

There is an increasing interest in utilizing historical data to supplement data from clinical trials. Potential applications of this approach include the replacement or augmentation of a control arm, extrapolation of

evidence to other populations (e.g. pediatric) and borrowing from real-world data sources (such as electronic health records, claims data, and patient registries). This session will dig into key open questions related to the use of historical data for drug approval including:

- Health Authority's positions and regulatory requirements
- Effective strategies for incorporating historical data into a clinical development plan
- Statistical methodologies for integrating historical data with newly generated clinical data.

Beyond the classical type I error: Bayesian metrics for Bayesian designs using informative priors

Gaëlle Saint-Hilary, CEO, Statistical Methodologist at Saryga

There is growing interest in Bayesian clinical trial designs with informative prior distributions, e.g. for extrapolation of adult data to pediatrics, or use of external controls. While the classical type I error is commonly used to evaluate such designs, it cannot be strictly controlled and it is acknowledged that other metrics may be more appropriate. We focus on two common situations – borrowing control data or information on the treatment contrast – and discuss several fully probabilistic metrics to evaluate the risk of false positive conclusions. Each metric requires specification of a design prior, which can differ from the analysis prior and permits understanding of the behavior of a Bayesian design under scenarios where the analysis prior differs from the true data generation process. The metrics include the average type I error and the pre-posterior probability of a false positive result. We show that, when borrowing control data, the average type I error is asymptotically (in certain cases strictly) controlled when the analysis and design prior coincide. We illustrate use of these Bayesian metrics with real applications, and discuss how they could facilitate discussions between sponsors, regulators and other stakeholders about the appropriateness of Bayesian borrowing designs for pivotal studies.

Navigating Challenges in RCT Conduct: A Novel Bayesian Adaptive Semiparametric Approach Handling Primary and Secondary Endpoints in Pediatric Trial Design

Danila Azzolina, Assistant Professor in Medical Statistics, University of Ferrara

Randomized Controlled Trials (RCTs) play a crucial role in assessing the safety and efficacy of interventions in pediatric populations. However, conducting RCTs in pediatric settings presents several challenges, such as limited sample sizes, ethical considerations, and the need to address multiple endpoints. This research proposes a groundbreaking approach to tackle these challenges in pediatric RCT design.

The proposed methodology leverages the power of the Bayesian adaptive design in handling simultaneously primary and secondary endpoints, as proposed by Gajewski and colleagues in 2022, by also incorporating B-Spline semiparametric priors (Bornkamp, 2009), allowing also for flexible incorporation of the historical information or expert opinion concerning the treatment effect (Azzolina, 2022). This adaptive design leads to dynamically updating the prior distribution based on accruing data, thus enhancing the efficiency and precision of treatment effect estimation.

The proposed Bayesian adaptive semiparametric approach offers several key advantages. Firstly, it addresses the small sample size issue often encountered in pediatric trials by incorporating existing expert knowledge or historical data through informative priors. Secondly, it simultaneously accommodates the evaluation of multiple primary and secondary endpoints, effectively handling the multiplicity issue and reducing the need for stringent adjustments. Additionally, this approach incorporates ethical considerations by allowing interim analyses and potential early stopping rules based on accumulating evidence. This proposed design ensures that the trial can be terminated early for futility or efficacy, minimizing unnecessary exposure of pediatric patients to ineffective or potentially harmful treatments.

To validate the performance of our methodology, we conduct a simulation study by assuming several scenarios in a trial design called two-endpoint adaptive, which stops early only if a criterion is met for primary and secondary endpoints. The approach focuses the final analysis on the primary endpoint but also ensures adequate data for the secondary analysis. The simulation results demonstrate the robustness and superiority of the proposed design over traditional frequentist approaches and other Bayesian methods concerning the power, trial duration, and type I error rate.

Furthermore, we illustrate the practical design application through a real-world case study, the REnal SCarring Urinary infEction Trial (RESCUE), a pediatric RCT characterized by several challenges in study conduct. The proposed Bayesian adaptive semiparametric approach could facilitate researchers and clinicians in overcoming the challenges of conducting trials with limited resources and ethical considerations by enhancing statistical efficiency, promoting early decision-making, and accommodating multiple endpoints by also offering a promising avenue for optimizing the design and success of pediatric clinical trials.

External information borrowing in hypothesis testing under potential heterogeneity

Silvia Calderazzo, Division of Biostatistics, German Cancer Research Center

In order to increase the efficiency of a clinical trial, leveraging of available external information about the control and/or treatment arm effect is often desired. The Bayesian approach allows borrowing of such external information through the adoption of informative prior distributions. Borrowing can improve testing and estimation if external information is consistent with the current trial's data-generating process, but losses can be severe otherwise. Several robust approaches have been proposed to limit the impact of potentially heterogenous external information. However, trade-offs in terms of frequentist characteristics are still present and in general no power gains are possible if strict control of type I error rate is desired. Moreover, such approaches require the choice of tuning parameters and/or distributions which, while fully characterized from a Bayesian viewpoint where prior beliefs have their own right, are often not intuitively related to their induced frequentist operating characteristics.

Aim of this talk is to provide an overview of the theoretical rationale underlying the impact of information borrowing on frequentist operating characteristics, as well as to present recent work on methodology which can allow principled and controlled type I error rate inflation in this context.

Bayesian model-informed analysis to estimate maintenance of efficacy

Guillemette de La Borderie, Principal Biostatistician at UCB

During the development of a drug in a rare disease, 3 studies were conducted: a phase 2 3-month double-blind placebo-controlled study, a phase 3 3-month, double-blind placebo-controlled study and an open-label extension study. A model-informed analysis (MIA) was used to estimate the maintenance of efficacy effect versus control up to 6 months using indirect comparisons in a Bayesian 2-part combined analysis:

Part 1: A Bayesian meta-regression using aggregate control response over time from different sources (systematic literature review and two external sources of individual patient data). The model included a study dependent intercept, centered log-time and centered baseline variables. Non-informative priors were used for all the parameters.

Part 2: A Bayesian informed combined-individual patient data analysis of the three clinical trials. The model included a study and subject dependent intercept, subject dependent centered log-time, centered baseline, study and subject dependent treatment, a centered log-time by treatment interaction and a shift parameter to model the shift from double-blind to open-label period. Informative robustified priors of the

mean control response beyond 3 months, derived from Part 1, were downweighed (for prior data conflict). Non-informative priors were used elsewhere.

This Bayesian 2-part combined analysis was run in RJags assuming either a log-linear and or an Emax (using functional uniform priors) evolution over time. This approach demonstrates that this MIA is a helpful methodology to support the development of new drugs in rare diseases where data from clinical trials are limited.

Bayesian dynamic borrowing approach for a meningitis B vaccine label update indicating its effectiveness against infections caused by Neisseria Gonorrhoeae

Elisa Cinconze, Principal Statistician, GSK

A systematic literature review on real-world and clinical studies on effectiveness of Meningitis B vaccine against gonorrhoea was performed and results were evaluated to be synthesized. Estimates from observational studies have been used as historical data in a meta-analytic approach. A Bayesian robust prior derived from the historical data is a mixture of a Meta-Analytic-Predictive (MAP) prior and a non-informative prior. The weights used for mixing the non-informative with the MAP priors have been set up to equal to 0.5. The mixed prior has been used for estimating the Vaccine Effectiveness (VE) of Meningitis B vaccine on gonorrhoea using the data of the DOXYVAC randomized clinical trial of Molina et al., and it was then used to obtain a VE posterior distribution with its 95% credible interval.

11th October 2023 - Forum

Better decision making in drug development through quantitative tools and innovative trial designs		**Giulia Zigon**
9.30 – 10.00	**A decision theoretic approach to assess the probability of success of an experiment**	Fulvio De Santis
10.00 – 10.30	**Probability of success calculation for vaccine efficacy trial in absence of correlate of protection: a method based on elicitation of correlate of protection model**	Valentino Conti
10.30 – 11.00	**Coffee Break**	
11.00 – 11.30	**A Bayesian multi-arm multi-stage clinical trial design incorporating information about treatment ordering**	Alessandra Serra
11.30 – 12.00	**Designing and Optimizing a Multi-Arm Multi-Stage Clinical Trial through Cloud-based Simulation Software**	Pantelis Vlachos
12.00 – 12.45	**Lunch Break**	
The estimands journey: from theory to practice		**Daniele Bottigliengo Andrea Nizzardo**
12-45 – 13.15	**Principal stratification: *principal stratum strategy* and beyond**	Silvia Noirjean
13.15 – 13.45	**Practical implementations of Estimands framework into clinical study protocols**	Elisa Rizzo
13.45 – 14.15	**The ICH E9(R1) estimand framework implemented in a phase III equivalence RCT conducted during COVID-19 pandemic: A Case Study**	Marian Mitroiu
14.15– 14.45	**Treatment policy estimand: A practical implementation to impute missing off-treatment data in a longitudinal study**	Andrea Vele
14.45 – 15.15	**Coffee Break**	
Real World Evidence to drive clinical and regulatory decision-making: challenges and solutions		**Giovanni Nattino Arturo Lanzarotti**
15.15 – 15.30	**SIMeF RWE working group**	Arianna Avitabile
15.30 – 16.00	**How to integrate primary and secondary data for Real-World-Evidence generation: an IQVIA 5-year experience in Italy**	Lucia Simoni Francesca Cassanelli
16.00 – 16.30	**Real-world data from Electronic Health Records to promote clinical research in Emergency Departments: the eCREAM project**	Fabiola Signorini
16.30 – 17.00	**Electronic Medical Records from a nationwide database of GPs surgeries to drive regulatory decision-making: case studies and analysis**	Riccardo Cipelli
17.00 – 17.30	**Considerations on the use of RWE in pharmaceutical development**	Roberta Bursi
17.30 – 17.40	**Closing**	IBIG Steering Committee

Better decision making in drug development through quantitative tools and innovative trial designs

Drug development is a learning process where new evidence accrued in clinical studies must be integrated with previously available information. New tools today exist to explore a variety of opportunities in order to improve the decision-making process. The implementation of the “model-based drug development”, with particular focus on the quantitative decision criteria, along with new adaptive designs aimed at making investment selections more efficient with an increased rate of treatment program success will be presented with practical examples and case-studies.

A decision theoretic approach to assess the probability of success of an experiment

Fulvio De Santis, Full Professor at University of Rome "La Sapienza" (joint work with Stefania Gubbiotti and Francesco Mariani)

In clinical trials a popular approach to sample size determination is based on the idea of "probability of success" of an experiment. However, there are several different ways to define and name such a probability of success, mainly based on suitable Bayesian elaborations on the distribution of the power function of a frequentist test induced by a design prior. We here provide a general and unifying decision-theoretic look at this problem. For their relevance in sample size determination, we also consider the asymptotic behavior of the quantities involved. The central role of the design prior is discussed.

Probability of success calculation for vaccine efficacy trial in absence of correlate of protection: a method based on elicitation of correlate of protection model

Valentino Conti, Associate Director, GSK

The quantification of how much early phase trials de-risk (i.e. increase the probability of success) later phases is a key quantitative tool for decision-making. Since in vaccines development early phase trials are usually based on immunological endpoints, a statistical surrogate is required to link immune response in early trials with efficacy in late phase. In the absence of available data to estimate a Correlate of Protection (CoP) model (i.e. a statistical model relating probability of infection with immunological endpoint), we elicited expert judgements to inform construction of CoP model for a candidate vaccine.

We leveraged the method proposed by Callegaro and colleagues* to use CoP model to calculate probability of success of Phase 3 efficacy trial based on immunogenicity result from Phase 2: given lack of CoP model, we extended Callegaro method with formal elicitation of CoP model, under the assumption that seroresponse induced by candidate vaccine is a statistical surrogate for efficacy against clinical endpoint.

The proposed method will be illustrated with artificial date, strengths and limitations will be discussed.

*Callegaro Andrea, Toufik Zahaf, and Fabian Tibaldi. "Assurance in vaccine efficacy clinical trial design based on immunological responses." Biometrical Journal 63.7 (2021): 1434-1443

A Bayesian multi-arm multi-stage clinical trial design incorporating information about treatment ordering

Alessandra Serra, Research Associate in Medical Statistics at University of Cambridge (joint work with Pavel Mozgunov and Thomas Jaki)

In this talk, we will present a Bayesian multi-arm multi-stage trial design that selects all the promising treatments with high probability and can efficiently incorporate the information about order in the treatment effects of the arms (e.g. when considering different treatment durations, different doses, or nested combination of treatments). A distinguishing feature of the design is that it allows taking into account the uncertainty of the treatment effect order assumption and it does not assume any parametric dose-response or duration-response model.

The focus of this talk will be on the implementation and evaluation of this design in a specific clinical trial setting. Specifically, we will cover how the decisions are made at each analysis and how the family-wise error rate and the power requirements are achieved. Via simulations, we will compare the proposed Bayesian design with the standard multi-arm multi-stage design and demonstrate the gains in the sample sizes the proposed design can provide. We demonstrate the robustness of the proposed design to violations of the assumptions on the order.

Designing and Optimizing a Multi-Arm Multi-Stage Clinical Trial through Cloud-based Simulation Software

Pantelis Vlachos, VP Cytel inc.

We present a case study that utilizes Solara to design a Multi-Arm Multi-Stage Trial. In this example design considerations covered will include allocation ratio, type-1 error, choice of multiplicity comparison procedure, interim analysis spacing, treatment selection methods and futility thresholds. In this talk you will learn:

- How cloud computing can be used to optimize a Phase II design, via a live demonstration
- Review simulation results and effective communications through visualizations
- How this type of optimization can reduce costs and shorten timelines for design and execution

The estimands journey: from theory to practice

The estimands framework has been introduced in 2019 by the Addendum to the ICH E9 guideline on statistical principles for clinical trials to improve alignment between clinical questions, objectives, design, and analysis of clinical trials. Since its release, the addendum has rapidly impacted the drug development world, triggering interest and discussions. Many efforts have been made to clarify the theory behind the framework to strengthen the interaction between relevant stakeholders and between sponsors and regulators. Now that the framework has started to be broadly adopted, several challenges have arisen during its implementation. The session will focus on experiences and case studies on practical issues encountered when adopting the framework in clinical trials.

Principal Stratification: principal stratum strategy and beyond

Silvia Noirjean, Statistical & Mathematical Modeling, GSK

In recent years, Principal Stratification (PS) has been in the spotlight. PS is a versatile framework introduced by Frangakis and Rubin (2002; hereafter FR) to evaluate the causal effect of a treatment or an intervention while accounting for the presence of post-treatment variables. As a matter of fact, a significant portion of the literature on this topic has been dedicated to leveraging PS to tackle treatment noncompliance. The recent release of the ICH E9 (R1) addendum, advocating the possibility of using the principal stratum strategy to address intercurrent events, and thus to construct the estimand, indicates that this trend is poised to continue. PS has also proven valuable in evaluating surrogates, leading to the development of a set of methods that started from the original definition of principal surrogate by FR but then went far beyond it. This presentation aims to provide an explanation of PS by exploiting, as an illustrative example, an application to a vaccine study.

Practical implementations of Estimands framework into clinical study protocols

Elisa Rizzo, Project Statistician, Chiesi Farmaceutici

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. In this presentation, using examples of clinical trials in COPD or Asthma, we try to clarify the practice behind the theory: opportunities and challenges in implementing the framework in protocols. Examples of proposals for handling treatment policy, hypothetical estimand, intercurrent events strategy and regulatory feedbacks on these will be presented.

The ICH E9(R1) Estimand Framework Implemented in a Phase III Equivalence RCT Conducted During COVID-19 Pandemic. A Case Study

Marian Mitroiu, Associate Director Biostatics, Biogen

Introduction and Objective(s): A multiregional Phase III equivalence study of proposed biosimilar BAT1806/BIIB800 vs reference tocilizumab, was conducted partially during the COVID-19 pandemic. As a consequence of COVID-19 pandemic and lockdowns, intercurrent events related or not to COVID-19 were identified. ICH E9(R1) estimand framework[1] with strategies for addressing these intercurrent events was implemented for efficacy evaluation following Regulatory recommendations[2].

Method(s) and Results: Primary estimand for EMA assessed the treatment effect at Week 12 where the clinical question of interest was: "What is the treatment effect had no subject discontinued the treatment, nor missed a study treatment infusion, for any reason, had rescue medication not been available (hypothetical), and death considered a non-response (composite)?".

Primary estimand for FDA/NMPA assessed the treatment effect at Week 24 where the clinical question of interest was: "What is the treatment effect regardless of any treatment discontinuation or missed study treatment infusion, regardless of any rescue medication need within protocolled window (treatment policy), and death considered a non-response (composite)?". Secondary estimands for Regulatory Agencies assessed the treatment effect at Week 12/Week 24 where the clinical question of interest was: "What is the treatment effect regardless of any treatment discontinuation or missed study treatment infusion not related to COVID-19 (treatment policy), and had no subject discontinued treatment or missed a study treatment infusion related to COVID-19 (hypothetical), and regardless of rescue medication need within protocolled window (treatment policy), and death considered a non-response (composite)?".

Faced with COVID-19, E9(R1) was helpful to define treatment effects using the estimand attributes, especially the strategies for addressing intercurrent events. The implementation of the estimand framework resulted in three different estimand constructs, primary or secondary, depending on recommendations from each Regulatory Agency.

Conclusions: The ICH E9(R1) estimand framework was implemented for a pivotal study following guidance and methodological considerations for trials possibly affected by COVID-19. Regulatory Agencies prioritised different estimands as primary, perhaps leading to giving different weight to outcomes more relevant to clinical practice, as opposed to sensitivity to detect differences between candidate biosimilar and reference in this equivalence study.

References:

[1] ICH E9(R1) EWG. Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials E9(R1)

[2] EMA. Implications of coronavirus disease (COVID-19) on methodological aspects ongoing clinical trials - Scientific guideline [Internet]. European Medicines Agency. 2020 [cited 2023 Feb 22].

Treatment policy estimand: A practical implementation to impute missing off-treatment data in a longitudinal study

Andrea Vele, Statistician, Chiesi Farmaceutici

Treatment policy is a strategy foreseen by ICH E9 addendum to address intercurrent events. When addressing treatment discontinuation, this strategy requires collecting key study data after the intercurrent

event (i.e. off-treatment data). Despite efforts in collecting off-treatment data, it's likely that some of the subjects will withdraw from the study, leading to missing data. Multiple imputation techniques are useful to handle missing off-treatment data. A practical SAS implementation proposed by O'Kelly and Li [1] will be presented for the case of a parallel study with longitudinal data collection of a continuous normally distributed endpoint. The aim of this procedure is to impute missing off-treatment data using the collected off-treatment data and to palliate the expected problem of sparsity in case of the amount of the collected off-treatment data is limited. An overview of the topic and the SAS code will be shown during the session.

Reference: [1] O'Kelly M and Li S (2022) Template code treatment policy estimand using SAS PROC MI and the MISTEP macro

Real-world evidence to drive clinical and regulatory decision-making: challenges and solutions

Real-world evidence (RWE) provides information about risks and benefits of medical products derived from patients' health data that are routinely collected in clinical practice, often referred to as real-world data (RWD). Sources of RWD include administrative data, medical claims, electronic health records and regional or national registries. While modern advancements in technology make these data increasingly available, the possibility to use RWD to derive strong RWE is hampered by a variety of factors, including concerns about privacy protection, the lack of structured clinical information and of clinically relevant outcome measures in the available datasets, the need of advanced statistical methods to infer effects in observational designs and the lower trust often attributed to RWE findings as compared to RCT results. In this session, we discuss RWE challenges and the role of statisticians to leverage RWD.

Lucia Simoni & Francesca Cassanelli, Medineos / IQVIA

How to integrate primary and secondary data for Real-World-Evidence generation: an IQVIA 5-year experience in Italy

Real World Data are information related to health status and healthcare resources utilization that are routinely collected from various sources. Primary data are directly and specifically collected for study purposes. On the other hand, secondary data are already available information. The combination of primary and secondary data is a powerful way to improve evidence generation process in a Real-World-Evidence (RWE) setting, through the set-up of the so-called enriched studies, exploiting the strengths of both data types to reduce their shortcomings. However, the data integration process brings possible challenges that need to be tackled to assure proper quality of generated insights. A presentation of practical cases will be done, and it will highlight critical issues of primary and secondary data integration and provide suggestions on how to overcome them.

Riccardo Cipelli, Medineos / IQVIA

Electronic Medical Records from a nationwide database of GPs surgeries to drive regulatory decision-making: case studies and analysis.

The use of secondary data to inform regulatory agencies on treatment pathways, outcomes research, and safety surveillance in Real-World settings has increased over the years. The IQVIA Longitudinal Patient Database (LPD) contains Electronic Medical Records (EMR) registered by around 900 General Practitioners uniformly distributed across Italy. This primary care database contains longitudinal data on demographics, clinical diagnoses, lab tests, referrals to specialists, and treatment prescriptions of more than 1,000,000 active patients' representative of the Italian general population in terms of age and gender. In this presentation, we will look at how evidence generated accurately analyzing LPD data can inform regulatory submissions.

Fabiola Signorini, Mario Negri

Real World data from Electronic Health Records to promote clinical research in Emergency Departments: the eCREAM project

Research in Emergency Departments (ED) has to cope with the unsustainability of data collection, due to the vast number of visits and lack of dedicated resources. A solution relies on the extraction of data from the electronic health records (EHR) of the EDs, avoiding dedicated, time-consuming data collections. However, the consistency of data extracted from EHRs is usually poor. In facts, while some data are structured, such as vital parameters, the most useful patient information is contained in free text. To address these problems and create high-quality clinical databases in EDs, the EU-funded eCREAM project will follow, in parallel, two different approaches. First, the project will develop technical solutions to extract reliable information from the EHRs already in place, using a Natural Language Processing (NLP) model to obtain information from free text. Second, a new EHR for the ED will be developed, to simultaneously meet organisation, clinical practice, and clinical research needs. To prove the practical validity of the extracted data on a highly relevant research question in emergency medicine, the data will be analysed to study the propensity of ED physicians to hospitalise patients arriving to the ED with dyspnea or transient loss of consciousness.