KEYNOTE

PRESENTATION TITLE: Presentations and discussion on real world evidence (RWE) used in regulatory decision-making

LEAD AUTHOR NAME/Email address: Nancy Santanello

SPEAKERS/AFILLIATIONS: To include: 1) Representative of FDA Center for Devices to present on Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices 2) Representative of FDA CDER to present on RWE in regulatory decision-making for drugs. 3) Representative of EMA to present on Regulatory Perspective on Real World Evidence (RWE) in scientific advice 4) Representative of Industry such as Cathy Critchlow or Brian Bradbury from Amgen to present on use of RWE in Regulatory decision for Blincyto or other product with RWE used in regulatory decisions. Panel consisting of FDA and EMA regulators, Industry and Database experts, and patient advocate to respond on the use of RWE for regulatory decision making.

SEMI-STRUCTURED ABSTRACT:

Topic: Presentations and discussion on real world evidence (RWE) used in regulatory decision-making.

Background/Problem being addressed: There are significant regulatory activities ongoing related to RWE. Under the 21st Century Cures Act (Cures Act), FDA is directed to develop a regulatory framework to evaluate how RWE can potentially be used to support approval of new indications for approved drugs or to support or satisfy post-approval study requirements. The FDA Center for Devices and Radiological Health and Center for Biologics Evaluation and Research have released a guidance on Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices The EMA has released Regulatory Perspective on Real World Evidence (RWE) in scientific advice. RWE can also be utilized for historical controls and to provide context for safety evaluation.

Approach: Four presentations to cover Regulatory RWE guidances and activities and an example from Industry of use of RWE in regulatory decision-making. Panel would respond to the presentations and discuss new uses of RWE in regulatory decision-making.

Learning objective/s: ISPE members and researchers would benefit from understanding guidances and activities in using RWE in regulatory decision-making, what types of data that could be used and how, methods of study design and conduct, human subject protections, and methods of analysis.

Rationale (Why is this topic of interest to the broad ISPE membership?): ISPE members should be at the forefront of use of RWE for regulatory decision making given the need for pharmacoepidemiology expertise in designing studies that will provide robust data to regulatory agencies.

PLENARY

PRESENTATION TITLE: "Implementation and Evaluation of Risk Minimization Measures: Challenges and Opportunities"

LEAD AUTHOR NAME/Email address: Rania Mouchantaf, PhD

SEMI-STRUCTURED ABSTRACT:

Topic: "Implementation and Evaluation of Risk minimization Measures: Challenges and Opportunities".

Background/Problem being addressed: In parallel with the global adoption of risk management planning, significant progress has been made in recent years in the area of risk minimization measures and evaluating effectiveness of such measures. These areas are now considered an integral part of pharmacovigilance. However adoption of such measures has also been accompanied with certain challenges and controversies. Examples include how to harmonize the risk minimization programs with regional or country-specific requirements, when should effectiveness be evaluated and what is an acceptable threshold rate to determine risk minimization success and, what is the role of the patients and health care professionals. In addition, more and more, it is recognized that evaluation of effectiveness should occur throughout the life cycle of a therapeutic product, and information is to be collected in real-world settings. This in turn will inform as to whether changes are needed to the product information or other terms of marketing including removal of regulatory requirements.

Approach: Considering that this is the 10^{th} anniversary to the global adoption of risk management planning (i.e., ICH E2E) worldwide, in this hot topic session, it is proposed to have four speakers each providing their perspective with focus on the elements highlighted above that are to be supported with case examples to illustrate real-world challenges and proposed solutions. Duration of each presentation is 15 minutes. The remaining 30 minutes will include a moderated discussion with the audience and a podium discussion with the panellists. The objective of the hot topic session is to generate a discussion and ultimately share best practices that can be used by all those who work or are implicated in the area of risk management planning.

Learning objective/s:

Upon completion of the session, the participants will be able to better understand:

- Similarities and differences in the approaches to implementing and evaluating effectiveness of risk minimization measures among the various regulatory agencies.
- Advancement in the area of risk minimization tools/dissemination in order to: a) facilitate their adoption into real-world clinical practice; b) make them more effective and; c) less burdensome.

- Effectiveness of risk minimization measures is a shared responsibility and all stakeholders involved need to be engaged. A discussion around the importance of patient and healthcare engagement will be presented in addition to new methodologies for measuring effectiveness of such measures.

Rationale Why is this topic of interest to the broad ISPE membership? (These sessions should be of interest to a wide audience.)This topic is of interest and will resonate to a broad audience that includes academia, industry, regulatory, health care professionals, patients and patient advocacy groups.

HOT TOPIC

PRESENTATION TITLE: Observational External Comparator Cohorts as Controls for Long-Term Uncontrolled Extensions to Randomized Clinical Trials for Regulatory Decision-Making

LEAD AUTHOR NAME: Nancy Santanello, MD, MS, FISPE

SEMI-STRUCTURED ABSTRACT:

Topic: Applying external observational cohorts as controls for long-term uncontrolled extensions to randomized clinical trials for regulatory decision-making

Background/Problem being addressed: Many Sponsors conduct long-term, open-label, uncontrolled Phase III extensions as part of their clinical trial development programs to collect long-term safety exposure and effectiveness data. These extensions can provide an efficient mechanism to gain long-term safety and duration of effect data while avoiding the ethical and practical considerations around long-term use of placebo. While these extensions offer benefits, there are also risks. A major risk derives from the uncontrolled nature of the follow-up, and the challenges it poses to the evaluation and interpretation of any unexpected serious adverse events (SAEs) that occur during the uncontrolled extension. The occurrence of even a small number of serious or otherwise clinically important adverse events may engender enough uncertainty with respect to the risk/benefit profile, that additional data may be required pre-submission, or lead to cautionary labeling, or prompt post-marketing safety study requirements.

The use of an observational, real world evidence (RWE) external patient cohort is a potential method to provide a control group for these open-label, long-term extensions that may mitigate some of the risks associated with such extensions. As the thinking of regulatory agencies evolves, the use of an external control cohort may become more acceptable in their decision-making.

Approach:

- Describe and discuss the scope, benefits and risks associated with the use of open-label, long-term extensions without a comparator group from the perspective of pharmaceutical industry.
- Present one or more examples of products where non-controlled, long-term extensions resulted in regulatory review issues.
- Describe and discuss the benefits and risks of evaluating comparative safety and/or ofeffectiveness using Real World external cohorts closely matched to patients enrolled in the original randomized clinical trial who continue treatment in an open-label, single arm, Phase III extension.
- Present where an external observational cohort to collect safety and/or effectiveness data were used to provide data to assist with regulatory decision-making.
- Evaluate best methods, databases, feasibility, utility, and economic impact of a concurrent, observational RWE external cohort for regulatory decision-making.
- Describe FDA and EMA regulatory guidances and/or positions related to the use of real-world, external cohorts as safety and/or efficacy comparators to long-term, open-label extensions of clinical trials.

Learning objective/s: As observational real-world evidence becomes more important for regulatory decision-making, this topic is important to pharmacoepidemiologists, pharmaceutical sponsors, regulators, database holders and users, clinical decision makers, payers, and patients.

Rationale: Why is this topic of interest to the broad ISPE membership? (These sessions should be of interest to a wide audience.)

Regulatory agencies are evaluating the use of real-world data in product development. As observational real-world evidence becomes more important for regulatory decision-making, this topic provides a specific application of real-world data in product development. The use of external-control groups for long-term uncontrolled extensions is important to those working with real-world data and evaluating their use, including pharmacoepidemiologists, pharmaceutical sponsors, regulators, database holders and users, clinical decision makers, payers, and patients.

For Hot Topic suggestions, what makes this "Hot"?

This topic will explore the use of external real-world cohorts to assist in understanding the safety and/or efficacy of a product prior to approval and assist in making regulatory decisions. Regulatory agencies are recognizing the importance of real-world data in regulatory decision-making. Many clinical trial programs are submitting long-term extensions of Phase III trials without a concurrent, internal control group. Since there are no guidance documents to help researchers and regulators determine how to construct and utilize external control groups and the best methods to employ, this session will provide new information to guide researchers.