Intelligent regulation and Statistics Promote the Modern Development of Regulatory Science in China

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Outline

- Overview of China’s growing focus on regulatory science, especially with AI.
- Statistical methods in modernizing regulatory processes.

Strengthening Regulatory Frameworks

- China has made significant advancements in strengthening its regulatory science landscape, especially in pharmaceuticals, medical devices, and healthcare.
- National Medical Products Administration (NMPA) have adopted international best practices to ensure product safety and efficacy.
- Emphasis on science-driven regulatory frameworks to support innovation and modernization.

AI and Advanced Technologies Integration

- Artificial Intelligence (AI), machine learning (ML), and big data technologies are at the core of China’s modern regulatory processes.
- China is utilizing AI to streamline drug approval processes and enhance post-market surveillance.
- Integration of real-world data and real-world evidence (RWE) into the regulatory decision-making process, making the regulatory system more adaptive and responsive.

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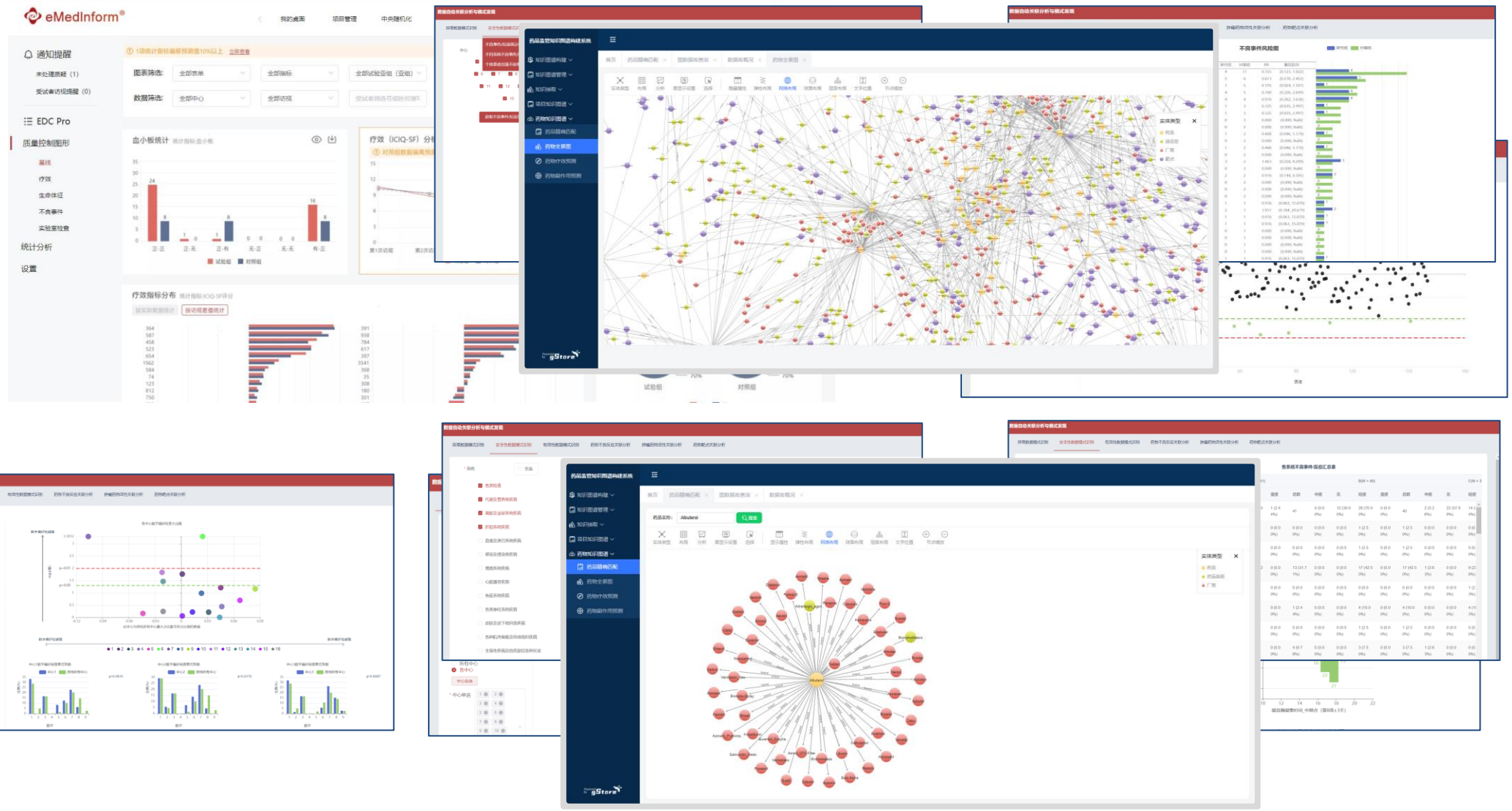

Focus on Innovation-Driven Regulation

- The regulatory shift towards innovation-driven frameworks allows for faster approval of novel therapies and medical devices.
- Emphasis on regulatory support for emerging areas such as gene therapies, cell therapies, and personalized medicine.
- China is leading efforts to create regulatory pathways that adapt to technological advancements, especially in biopharmaceuticals and digital health.

AI's Role in Regulatory Science

- - AI in Drug Discovery and Development: How AI accelerates candidate identification and clinical trial assessments.
- - Safety Surveillance: AI-powered systems for monitoring real-time data on adverse drug reactions (ADRs).
- - AI-Driven Precision Medicine: AI supports personalized medicine and diagnostics frameworks.

Strategic Challenges

- - Data Privacy and Security: Ensuring data protection while using AI for regulatory decisions.
- - Talent and Infrastructure: The need for a skilled workforce and AI infrastructure to support the evolving regulatory landscape.
- - Algorithmic Transparency: Ensuring AI-driven decisions are fair, ethical, and transparent.

New Methods and Technologies

- - Model-Informed Drug Development (MIDD): Use of statistical models to predict clinical outcomes and optimize trial designs.
- - Bayesian Adaptive Trials: Increasing flexibility and reducing development timelines.
- - Real-World Evidence (RWE): Using AI to analyze healthcare data and generate actionable insights for regulatory decisions.

Statistical Collaboration: Meeting ICH E17 Standards

- Tripartite Collaboration for Statistical Excellence:
  - Academia: Leveraged academic experts from Peking University and other top institutions to build a robust statistical framework.
  - Industry: Collaborated with pharmaceutical and biotech companies to ensure the developed models were practically feasible and met industry needs.
  - Regulators: Engaged with regulatory bodies to ensure that the statistical models and methodologies were compliant and could be incorporated into regulatory assessments.
- Unified Approach: This collaboration resulted in a unified approach to statistical analysis, aligning academic rigor, industry application, and regulatory requirements.

Tripartite Collaboration & Outcomes in Implementing ICH E17 in China

- Three Industry Bluebooks:

A culmination of shared insights and expertise, these bluebooks serve as comprehensive guides for academia, industry, and regulators.

Emphasize the statistical nuances, practical applications, and regulatory insights of ICH E17 in China's context.

- International Publications:

Collaborative discussions and findings were not just limited to local publications. The tripartite body made significant contributions by publishing their research in internationally renowned journals.

KEY Achievement--International Publicaitons

- Basic Considerations for Consistency Evaluation in Multi-Regional Clinical Trials (MRCT)
- Basic Considerations for Pooling Strategy in Multi-Regional Clinical Trials (MRCT)
- Basic Considerations for Planning and Implementing Extension Enrollment Strategies in Multi-Regional Clinical Trials (MRCTs)

Basic Considerations for Consistency Evaluation in MRCT

- **1. Background and Objective**
  - 1.1 About ICH E17
  - 1.2 Consistency Evaluation in the Context of ICH E17
  - 1.3 Consistency Evaluation and Combined Strategy
  - 1.4 Consistency Evaluation and Regional/Country Sample Size Allocation

Basic Considerations for Consistency Evaluation in MRCT

- **2. Considerations at Different Stages**
  - 2.1 Design and Planning
  - 2.1.1 Epidemiology
  - 2.1.2 Overview of Disease Diagnosis and Treatment
  - 2.1.3 Clinical Pharmacological Studies and Dosage
  - 2.1.4 Intrinsic and Extrinsic Ethnic Factors
  - 2.1.5 Combined Strategy
  - 2.1.6 Regional Sample Size Allocation

Basic Considerations for Consistency Evaluation in MRCT

- **2.2 Execution**
- **2.3 Results**
  - 2.3.1 Interpretation of Overall Evidence
  - 2.3.2 Three-Tier Approach
  - 2.3.3 Clinical Pharmacology (Including PK and PD)
  - 2.3.4 Efficacy/Pharmacodynamics
  - 2.3.5 Safety Consistency Evaluation
  - 2.3.6 Benefit-Risk Consistency Evaluation

Basic Considerations for Consistency Evaluation in MRCT

- **3. Special Considerations**
  - Non-inferiority
  - Multiple Primary Endpoints
  - Interim Analysis
  - Delayed Effects
  - Adaptive Designs
  - Rare Diseases
  - Statistical Analysis Models

Basic Considerations for Consistency Evaluation in MRCT

- **4. Exploratory Framework in Cases of Possible Deviations from Expectations**
  - Clinical Relevance
  - Disease and Treatment
  - Clinical Pharmacology
  - Biological Justifiability
  - Enrollment and Sample Size
  - Baseline Characteristics
  - Exposure, Follow-up, and Distribution
  - Internal/External Consistency
  - Statistical Uncertainty

Enhancing Success Probability: A Statistical Perspective on Clinical Trials and Drug Development

- Esophageal cancer cancer trials face several unique challenges:
  - Prevalent in China with unique etiology but not in western country
  - Difficulty in early detection and diagnosis
  - Low overall survival rate (less than 5 years)

- The nature of this cancer leads to difficulty in achieving large effect size.
  - **Larger sample sizes are required to detect a small differences**.

- Early stopping in multiple interim analysis has known side effects:
  - Stopping for efficacy → reduce the actual power
    - Low P-value threshold and large sample size accumulate may mitigate this issue.
  - Stopping for futility → increase the type I error.
    - Often need to be controlled by beta spending functions or conditional power.

Practical concerns in GI cancers

- **Can we use short-term endpoint to predict the long-term endpoint?**
  - The answer determines the types of dual endpoints to be integrate into the study.
  - This action may be study types dependent:
    - ORR and PFS are not sufficiently correlated with OS in advanced gastric cancer population (Shitara et. al, 2014).
    - In molecular enriched population (oncogene-driven cancer), OS are highly correlated with PFS, and weakly correlated with ORR (Solomon et. al, 2022).
    - ORR varies by markers in different types of therapies.

- **Do we care about hazard ratio (HR) or median survival as the quantitative measure?**
  - The answer determines how we choose our modelling scheme.

Futility interim analysis using a surrogate endpoint in colorectal cancer

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- Historical relationship between surrogate endpoint and overall survival is established in this paper.
- This method is applied to design a Phase III clinical trial in metastatic colorectal cancer.
  - OS –> primary endpoint
  - PFS –> surrogate endpoint

ABSTRACT

In clinical trials with time-to-event data, the evaluation of treatment efficacy can be a long and complex process, especially when considering long-term primary endpoints. Using surrogate endpoints to correlate the primary endpoint has become a common practice to accelerate decision-making. Moreover, the ethical need to minimize sample size and the practical need to optimize available resources have encouraged the scientific community to develop methodologies that leverage historical data. Relying on the general theory of group sequential design and using a Bayesian framework, the methodology described in this paper exploits a documented historical relationship between a clinical "final" endpoint and a surrogate endpoint to build an informative prior for the primary endpoint, using surrogate data from an early interim analysis of the clinical trial. The predictive probability of success of the trial is then used to define a futility-stopping rule. The methodology demonstrates substantial enhancements in trial operating characteristics when there is a good agreement between current and historical data. Furthermore, incorporating a robust approach that combines the surrogate prior with a vague component mitigates the impact of the minor prior-data conflicts while maintaining acceptable performance even in the presence of significant prior-data conflicts. The proposed methodology was applied to design a Phase III clinical trial in metastatic colorectal cancer, with overall survival as the primary endpoint and progression-free survival as the surrogate endpoint.

https://doi.org/10.1002/pst.2410

How to integrate prior knowledge into the ongoing trial?

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- Two types of information borrowing in Bayesian statistics:
  - Borrowing effect size from from similar studies, β, similar to meta-analysis.
  - Borrowing the survival curve, e.g. test-and-pool, commensurate prior

- We want to decide on the statistical method on information borrowing:
  - Drugs with the same mechanism?
  - Data for the same drug from previous phases?
  - Different tumor subtypes matters?
  - Do treatment schemes bring in disparities across study designs?
  - Do we have clinical vs. statistical significance for the endpoint we studied?

- Lastly, we might want to control the confounders across the studies.

Conclusion

- AI and statistical methods are revolutionizing regulatory processes.
- Importance of global collaboration for AI and statistical tool development.
- The future of regulatory science relies on the integration of these technologies.

Thanks for your attention!

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