CHANGES IN FIRST-IN-HUMAN TRIALS - NEW ERA OF DEMANDING HEALTHCARE RESEARCH

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JANUARY 2017
The European Medicines Agency will be updating its guideline on first-in-human clinical trials in 2017. The most important anticipated impact of the revised guideline will be the enhancement of its current strategies to identify and mitigate risks for trial participants to conduct trials in a safe, efficient and transparent manner to the benefit of public health. Global Compliance and Quality Director Jessica Santos, Ph.D., explains the new guideline and what it will mean for pharmaceutical companies.

THE EUROPEAN MEDICINES AGENCY (EMA) IS PLANNING TO UPDATE ITS GUIDELINE ON FIRST-IN-HUMAN CLINICAL TRIALS. CAN YOU SUMMARIZE THE PROPOSED CHANGE?

While the 2007 guideline focused on the single-ascending-dose design used at that time, the practice for conducting first-in-human clinical trials has evolved toward a more integrated approach, with sponsors conducting several steps of clinical development within a single clinical trial protocol (e.g., to assess single and multiple ascending doses, food interactions, or different age groups).

The proposed guideline outlines strategies to mitigate and manage risks for trial participants, including principles to be used for the calculation of the starting dose in humans, the subsequent dose escalation, and the criteria for maximum dose, as well as principles on the conduct of the clinical trial, including the conduct of studies with multiple parts.

In particular, guidance is proposed on non-clinical aspects such as the better integration of pharmacokinetic and pharmacodynamic data and toxicological testing into the overall risk assessment, as well as the role of non-clinical data in the definition of the estimated therapeutic dose, maximal dose, and dose steps and intervals. Guidance is also provided on clinical aspects, including criteria to stop a study, the rolling review of emerging data with special reference to safety information for trial participants, and the handling of adverse events in relation to stopping rules and rules guiding progress to the next dosing level.

1. Extension of the guidance to early-phase clinical trials, including single study or integrated protocol designs

2. Extension of the non-clinical aspects of the guideline to address:
   a. Better integration of non-clinical pharmacology data (including pharmacokinetic and pharmacodynamic data evaluated using current pharmacokinetic/pharmacodynamic or physiologically based pharmacokinetic modeling) and data from the toxicology testing into an overall risk assessment for first-in-human and early clinical trial administration
   b. Translation of non-clinical data to human use by extrapolation and verification of assumptions made
   c. Expanding on the minimum anticipated biological effect level (MABEL) approach taking all biological effects into account
   d. Role of non-clinical data for:
      i. Estimated therapeutic dose, maximum human dose level (both for single ascending dose and multiple ascending dose parts), dose escalation steps, and dosing frequency and intervals
THE NEW GUIDELINE REFLECTS THE EVOLUTION OF PRACTICES IN THE LAST 10 YEARS AND TAKES INTO ACCOUNT THE TRAGIC PHASE I TRIAL IN FRANCE LAST YEAR.

ii. Definition of stopping criteria for the trial

iii. Identification of safety aspects to monitor

3. Extension of the clinical part of the guideline with new guidance to address:

a. Integrated clinical trial designs and study endpoints, including decision-making aspects

b. Extension of the remit of the guidance beyond single-ascending-dose first-in-human trials to incorporate other early-phase trials and designs

c. Clarification on the choice of trial subjects

d. Overall dose/exposure range and scheme, including stopping rules

e. Rolling review of emerging human data during the study

f. General principles on key scientific information to be included in a clinical trial application

g. Safety observations for trial participants

h. Handling of adverse events in relation to stopping rules and progress to next dosing steps

i. General principles on communication to competent authorities and clinical subjects

WHY DO YOU THINK THE CHANGE IS HAPPENING?

Clinical trials are essential for the development of medicines, and without them patients cannot gain access to new, potentially life-saving medicines. EU and international guidelines are in place to ensure that first-in-human clinical trials are conducted as safely as possible. The EMA’s existing guideline, released in 2007, provides advice on first-in-human clinical trials, in particular on the data needed to enable their appropriate design and allow the initiation of treatment in trial participants.

The new guideline outlines the major areas that needed to be revised to reflect the evolution of practices in the last 10 years. The review also took into account the lessons learned from the tragic incident that took place during a Phase I first-in-human clinical trial in Rennes, France, in January 2016. In this trial of BIA 10-2474, an experimental fatty acid amide hydrolase inhibitor that interacts with the human endocannabinoid system, serious adverse events occurred in five participants (including deep hemorrhagic and necrotic lesions), including the death of one man.

HOW IS THE REVISION LIKELY TO AFFECT THE PHARMA COMMUNITY AND REAL-WORLD RESEARCH COMPANIES?

The revision is intended to further assist sponsors in the transition from non-clinical to early clinical development and identifies factors influencing risk for new investigational medicinal products (IMPs). The document includes considerations on quality aspects, non-clinical and clinical testing strategies, and designs for first-in-human clinical trials and early-phase clinical trials. Strategies for mitigating and managing risks are given, including principles on the calculation of the starting dose to be used in humans, the subsequent dose...
SAFETY, MINIMIZING RISK, AND BETTER INTEGRATED USE OF DATA DOMINATE THE CHANGE; THESE DEMANDS WILL EXTEND BEYOND FIRST-IN-HUMAN CLINICAL TRIALS.

Pharma companies conducting first-in-human trials will soon need to adopt the new guideline in their trial design, execution, and monitoring. Trials will not necessarily last longer, but they will require closer monitoring of participants, so costs will rise. For example, instead of staff checking on participants every four hours, as may have been acceptable in the past, participants may need to be checked every hour or more frequently to monitor for any serious adverse events. Real-world research practitioners should expect to produce more supporting data and detailed calculations to back up any study design, especially in interventional studies, where the risk to participants is higher.

WILL THIS HAVE FAR-REACHING EFFECTS ON OTHER ASPECTS OF REAL-WORLD AND CLINICAL RESEARCH IN ADDITION TO FIRST-IN-HUMAN CLINICAL TRIALS?

Safety, minimizing risk, and better integrated use of data dominate the change. I do expect these demands will extend beyond first-in-human clinical trials. Here are some possible consequences.

+ Data transparency requirements are strengthening while protecting patient privacy. As a result, methods of anonymization not only need to be considered but and clearly defined and adopted in study design.

+ Research Ethics Committees will demand more data and independent review before grant approval, especially on safety and risk minimization measures.

+ Study design will need reference publications and data as compulsory requirements, not just based on theoretical level.
REFERENCES


ABOUT THE AUTHOR

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Dr. Jessica Santos is the Global Compliance and Quality Director at Kantar Health, the largest custom market research company focused on the life sciences industry. She is primarily responsible for providing oversight and support across the 40+ Kantar Health global offices in the areas of regulation, interaction with clients, suppliers and others within Kantar Health, Kantar and WPP. Dr. Santos is responsible for maintaining, anticipating and coordinating all activities with regard to compliance laws/regulations, industry guidelines, pharmacovigilance and client contracts, defining and driving the execution of Kantar Health’s Quality Strategy – our approach to measuring and improving our quality efforts.

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