Regulatory Concerns and Challenges During and After the Covid-19 Pandemic: FDA Office of Cardiovascular Devices Perspective

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Disclosure Statement

Bram Zuckerman, MD has no relevant disclosures

Cardiovascular Device Trials pre-COVID-19

Twenty-first century has brought significant changes to the healthcare environment

Need for clinical trials ecosystem to adapt to these new realities

Many concerns and roadblocks about doing things differently

Pace of adaptation and change has not been optimal

Major Impact of Covid-19 on Device Clinical Trials

- Most ongoing trials have been paused at least once
  - Highest priority has been on patient and research staff safety
- Many restarts in progress
- Delays in enrollment and trial completion
- More missing or out-of-window assessments
- Protocols and Statistical Analysis Plans being altered
- Risk-based approaches to clinical trial data monitoring and audits being considered
- Best practices are being considered in real time

FDA Perspective on Cardiovascular Device Trials during and after COVID-19

- Landscape has definitely changed
- It is even more critical to adapt to new realities in an efficient manner
- Multiple stakeholders ***including patients*** need to be involved in this process to achieve success
- No fundamental FDA constraints on such an effort
- Rather knowledge of FDA expectations is required
- ***FDA strongly encourages modernization and optimization of the clinical trials ecosystem during this emergency and beyond***

FDA Device Approval Basics in the Covid-19 Era

- Device approval standards have not changed
- Rigorous design and execution of clinical trials, analytical integrity, and complete and prompt reporting of prespecified analyses are bedrocks of the process
- A robust post-approval system is needed to maintain timely access to safe and effective devices in the US
- Coordination with CMS remains critical for reimbursement decisions
- ***Within this context many options can be considered for improving and/or modifying the system***

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

March 2020

Updated on June 3, 2020

https://www.fda.gov/media/136238/download

Appendix: Questions and Answers

Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency

Guidance for Industry

June 2020

https://www.fda.gov/media/139145/download

- Trial integrity
  - Data collection for endpoint ascertainment changes
  - Approaches to minimize bias
- Trial mitigation and analysis strategies
  - Events related to COVID-19
  - Considerations for trial termination
  - Interim analyses
  - Missing data analyses
  - Trial endpoint modification

A Note on Covid-19 FDA Guidance Documents

- Key general principles outlined
- Provide starting points for consideration
- Dynamic environment requires efficient and regular communication among sponsors, investigators, statisticians, and FDA
- ***For specific scenarios be practical, logical, reasonable and flexible***

More Specific Discussion Needed in Heart Valve Disease Space to Develop Best Practices

Screening and enrollment

Covid and Disease Specific CRFs

Maintenance of F/U visits

Laboratory testing and diagnostic imaging

Risk Based Trial Monitoring

Use of Tele-Health

Statistical methods for sample size reestimation, handling missing data, dealing with confounding effect of Covid-19 on key endpoints

Covid-19 CEC and DMC SOPs

Additional Thoughts

- Multiple reasons why there has been significant resistance, disincentives and barriers to changing the clinical trial ecosystem
- Need to consider how to remove these legal, financial and cultural barriers
- Validating new ideas and practices through stakeholder collaboration may be one method for removing barriers
- ***Enabling patients to directly take an active part in development of a more patient-centric system is another key component***

What Success Looks Like

- Develop an improved Heart Valve Disease Learning Health Care Ecosystem for all Americans
- Discuss and develop proposals for high-quality clinical trials and research without overburdening research and hospital staff and study participants
- Commitment to continue this process – we will need to continue to reevaluate to optimally reshape the system
- Integrate new Tele-Health capabilities into this Ecosystem


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