Diversity in Medical Device Trials: Experiences From the Field

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Clinical Trials: Assessing Safety and Efficacy for a Diverse Population

Today’s Objectives
• Share with FDA and the public an example of how one company, Boston Scientific, has operationalized the principle of diversity in clinical data collection.

Background
• Product performance data must be reflective of the population at risk.
• The approach to demographic subgroup analyses in implantable medical devices has evolved over time (FDASIA 907).
• Barriers to clinical trial participation in implantable medical devices are similar to those encountered in other therapeutic areas.
• Disparities in clinical trial enrollment mirror the disparities in treatment.
• Analysis of premarket and post-market data can assure safety and efficacy are met in the entire population.
People of color are expected to represent over half (52%) of the U.S. population by 2050.
Disparities in Clinical Practice are Mirrored in Clinical Research

Women comprise 30% of PCI procedures and PCI clinical trial enrollment

PCI Procedures 2009
Patients: N=596,000

Gender Representation in PCI Clinical Trials

- Women: 34%
- Men: 66%

TAXUS-IV
- Men: 72%
- Women: 28%

SPIRIT III
- Men: 69%
- Women: 31%

SIRIUS
- Men: 71%
- Women: 29%

ENDEAVOR
- Men: 77%
- Women: 23%

National Hospital Discharge Survey/National Center for Health Statistics, 2009 Estimates are based on a sample of inpatient records from short-stay hospitals in the United States.

Heart Disease and Stroke Statistics-2012 Update. Circulation. http://circ.ahajournals.org/content/125/1/e2
Disparities in Clinical Practice are Mirrored in Clinical Research

White people comprise ~80% of PCI procedures and PCI clinical trial enrollment

Boston Scientific ION and LIBERTE Post-Market Studies: Pooled Patient Demographics

Composition (%) Registry | US
---|---
Other 0.8 | 6
Pacific 0.16 | 0.2
AI/AN 0.2 | 0.9
Asian 0.5 | 5
Latino 4 | 16
Black 7.5 | 13
White 86 | 72
Overall N=5305

FDA Safety and Innovation Act Sec. 907 Timeline

Workshops on Gender Differences in Cardiovascular Device Trials June and December, 2008

FDA Draft Guidance for Evaluation of Sex Differences December, 2011

FDASIA Sec 907 Enacted July 2012

FDA Report on Subgroup Representation in Clinical Trials August 2013

Public Hearing on FDA Action Plan April, 2014

FDA Final Guidance: Evaluation of Sex-Specific Data in Medical Device Clinical Studies August, 2014

FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data August, 2014

Drug Snapshot Page November, 2014

FD Public Meeting on FDASIA § 907

Anticipated Events

Draft Guidance on analysis and reporting of race, ethnicity and age in medical device clinical trials
Drug Eluting Stent Thrombosis
Coronary Revascularization Trends in the United States, 2001-2008

JAMA. 2011;305(17):1769-1776
2003 FDA approves first drug eluting stent

- Pivotal pre-market study of 1,100 patients in the SIRIUS trial

2005 concerns regarding DES late stent thrombosis surface

- Rare (~1.5%), catastrophic event (up to 50% mortality)
- Swedish Coronary Angiography and Angioplasty Registry ~20,000 pts
- Numerous meta-analyses and scholarly reports on DES outcomes.

2006 FDA convenes meeting regarding dual antiplatelet therapy (DAPT) duration

- DAPT duration extended to 1 year for DES.
2009 FDA Critical Path Initiative launches DAPT Study

- Unprecedented collaboration between 4 DES, 4 antiplatelet drug manufacturers and Harvard Clinical Research Institute.
- 2014 Primary endpoint announced: 11,648 pts; 30 vs 12 month DAPT following DES lowers ST and MI but raises bleeding rate.

Higher ST rate in African Americans observed in real-world registries

2009 Washington Hospital Center reports double rate of ST in Blacks

- 2012 Taxus Ethnicity meta-analysis confirmed registry data using randomized control trial data from robust Taxus database.

Black vs. White: Risk of MI and Stent Thrombosis

Batchelor et al. J Interv Cardiol 2012
2014 Boston Scientific launches Platinum Diversity study of women and minorities receiving DES

- Enrollment completed 3 months ahead of expected.
- Results expected late 2016.
What have we learned?
Potential Barriers to Research Participation

**Patient Pathway**

- **Patients not aware and/or not asked to participate**
  - Physicians ask women and minorities less often
  - Female symptoms misdiagnosed
  - Women and minorities not referred to specialist or treated in a setting with no access to research

- **Patient misunderstands potential risks and benefits**
  - Poor physician communication

- **Patient initially interested but does not enroll**
  - Patient does not meet criteria or has too many comorbidities to be a good candidate

- **Patient cannot execute participation logistics**
  - Clinic inefficiencies create patient burden

**Physician Sources**
- Patients not aware of opportunities
- No (or limited) access to internet
- Women are older than men at disease onset

**Patient Sources**
- Patients misunderstand risks and benefits
- Lack of patient educational materials
- Cultural biases
- Intimidated by terminology ("clinical trial" vs. "health research")
- Patient or family intimidated by consent form or trial materials
- Insurance coverage creates financial burden
- Comorbidities reduce interest
- No time, logistical burden, or caregiving responsibilities
- Caregiving responsibilities
- Cost of travel, lost wages, or child care
- Extra clinic visits
- No time
- No transportation
Opportunities for Change

1. Increase **awareness** around participation opportunities
   - Patient-focused awareness around the benefits of participation
   - Make it easier for patients and physicians to locate research opportunities (e.g. database)
   - Tools to increase awareness of participation opportunities among PCPs and General Cardiologists
   - Leverage physician societies and social networks to encourage women and minorities to participate (through interaction with their peers who have participated, etc)

2. Examine **trial design elements/protocols** and propose changes to increase the number of women and minorities who qualify

3. Reduce the **perceptions and misperceptions** around participation risk
   - Patient education materials that describe the research process as well as the benefits of participation
   - Education for investigators and trial coordinators on how to more effectively approach and communicate with female and minority patients

4. Leverage current **investigator database** to understand patient demographics with respect to clinical practice
   - Understand characteristics of demographic enrollment (which sites provide diverse enrollment, where do diverse patients reside, who manages the subgroup in question)
   - Close the Gap approach

Each of these opportunities requires participation from multiple stakeholders
Closing Thoughts

• **Pre-market data collection representative of investigator clinical practice**
  – Sufficient safety and efficacy data to allow device approval for broad population.
  – Assures device availability to general public is not delayed by lengthy enrollment timelines.

• **Post-market surveillance to provide data for subgroup analysis**
  – Variances in safety or efficacy may be identified during post-market clinical experience
  – Statistically relevant sample related to specific demographic subgroup are available for evaluation.

• **Additional analytic modalities to focus on specific subgroups**
  – Meta-analyses
  – Collaborative partnerships (e.g. NIH, CMS, HCRI)
  – Hypothesis generating studies

• **Leveraged data from existing sources such as SSED and Clinicaltrials.gov should be kept within the context from which the data were collected.**

• **Boston Scientific appreciates FDA’s openness to share internal practices and thinking. Interactive initiatives supporting FDASIA 907 action plan allow industry and FDA to align on key concepts which will result in better decision making and compliance.**