A Path from RWD to RWE – Stopping Over at Statistical Inference

ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop 2018

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Outline

- Cook Medical
- Motivating example of a post-approval study (PAS)
- Real world data (RWD)
- Pursuing a real world evidence (RWE) project
- Additional discussion topics

EARLY BEGINNINGS

Cook Medical

Began with 3 products and 2 employees in 1963.

Cook Medical

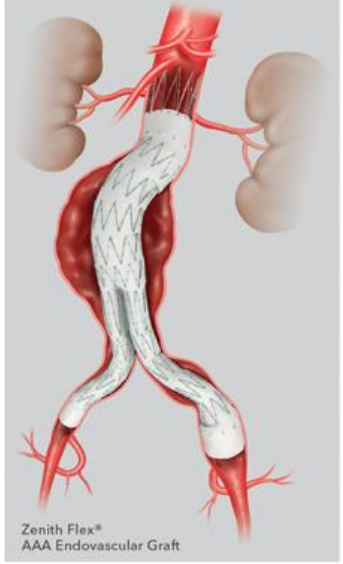
2
Divisions

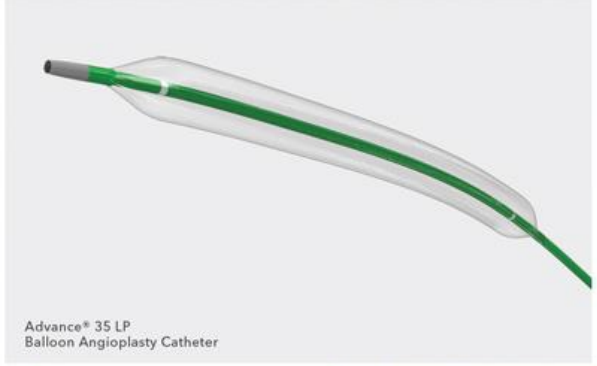
16,000
Products

10
Business units

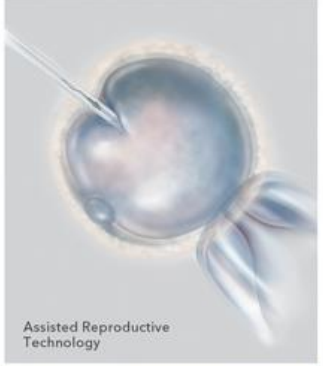
450
Product families

42
Medical specialty areas

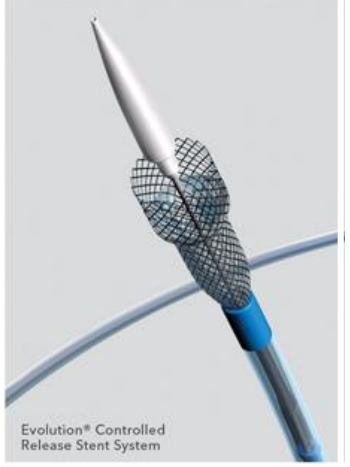

Zenith Flex®
AAA Endovascular Graft

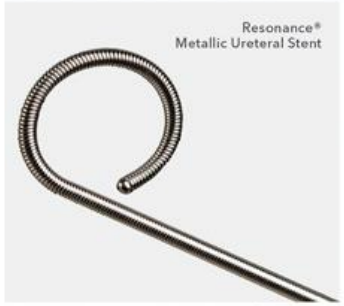

Advance® 35 LP
Balloon Angioplasty Catheter

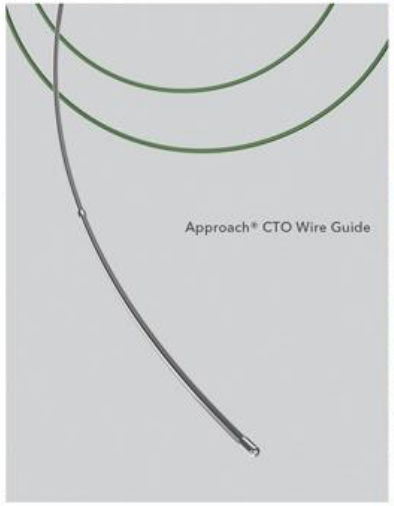

Coda® Balloon
Catheter


Assisted Reproductive
Technology


Zilver®
Self-Expanding Stent


Evolution® Controlled
Release Stent System

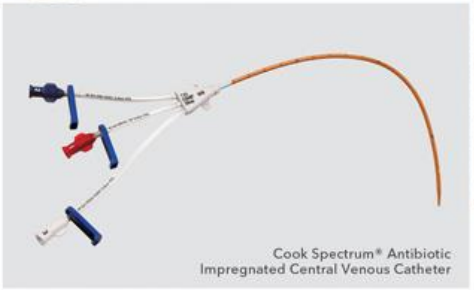

Resonance®
Metallic Ureteral Stent


Approach® CTO Wire Guide


Evolution® Mechanical Dilator Sheath

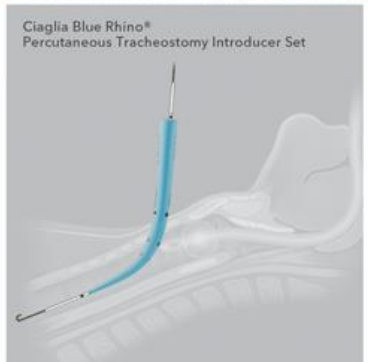

Angiographic Catheters

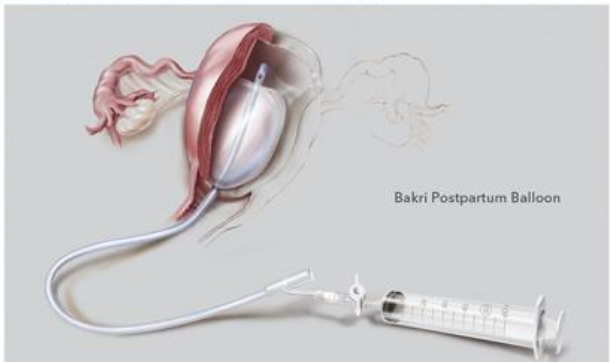

Günther Tulip® Vena Cava Filter


Cook Spectrum® Antibiotic
Impregnated Central Venous Catheter


Embolization Coils


Flexor® DL Dual Lumen Ureteral Access Sheath


Ciaglia Blue Rhino®
Percutaneous Tracheostomy Introducer Set


Bakri Postpartum Balloon

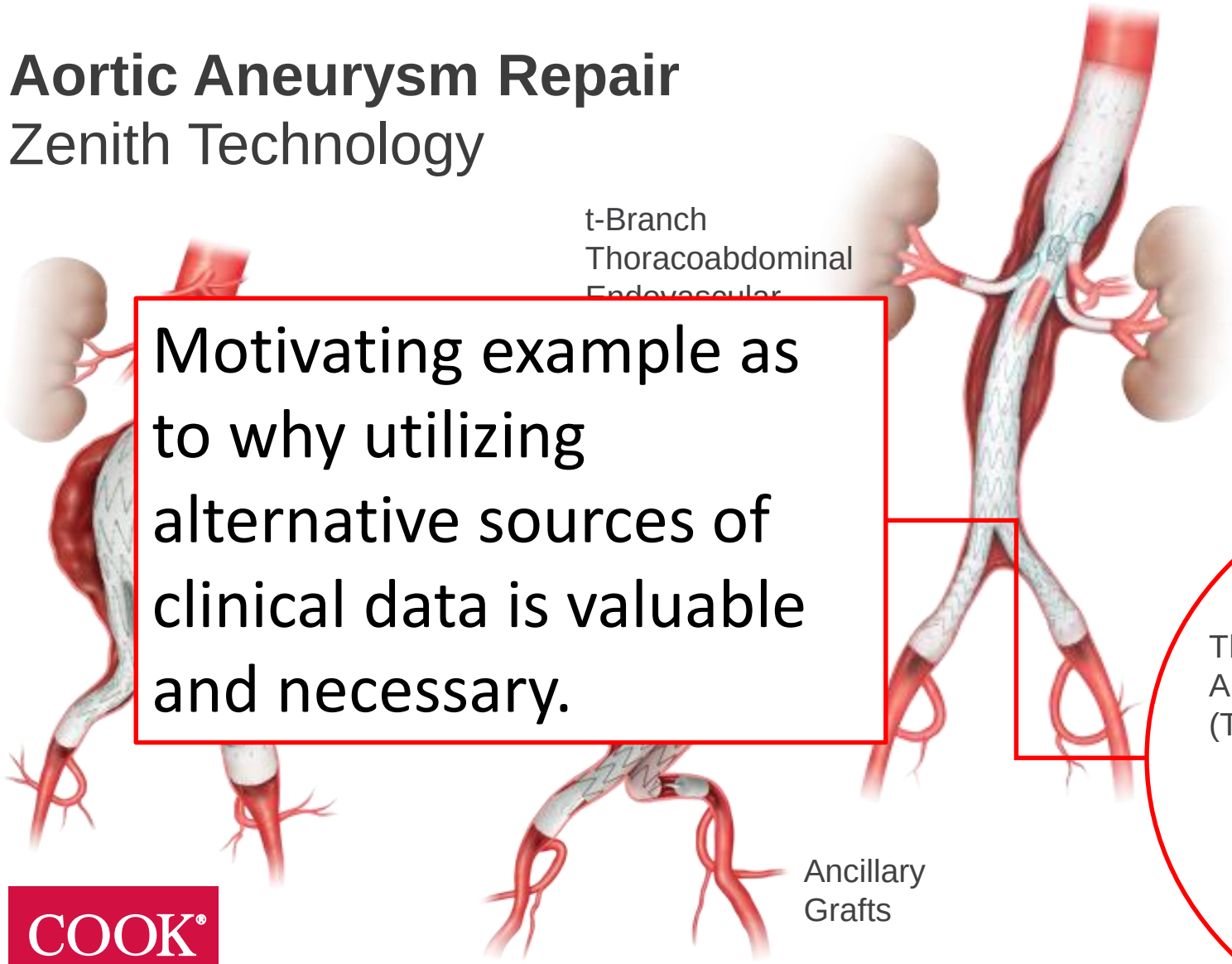

Percutaneous
Drainage Catheters

Mission Statement

Cook is dedicated to
bold leadership
in pioneering
innovative medical
solutions
to enhance patient care
worldwide.

Motivating Example

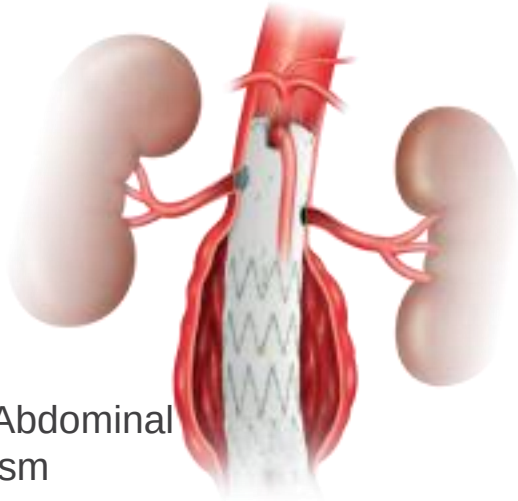
Aortic Aneurysm Repair
Zenith Technology



t-Branch
Thoracoabdominal
Endovascular

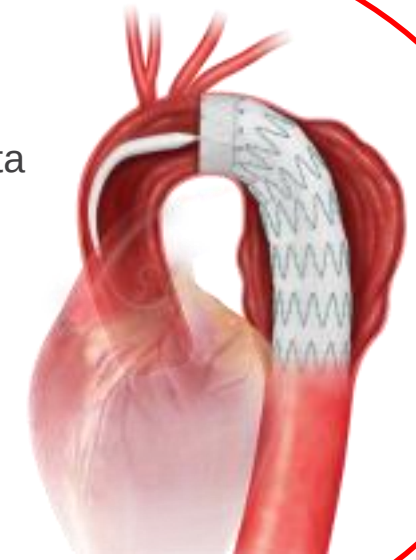
Motivating example as to why utilizing alternative sources of clinical data is valuable and necessary.

Ancillary
Grafts



Fenestrated Abdominal
Aorta Aneurysm
(AAA) Grafts

Thoracic Aorta
Aneurysm
(TAA) Grafts



COOK® MEDICAL

Example 1: Condition of Approval Study — Zenith® TX2®

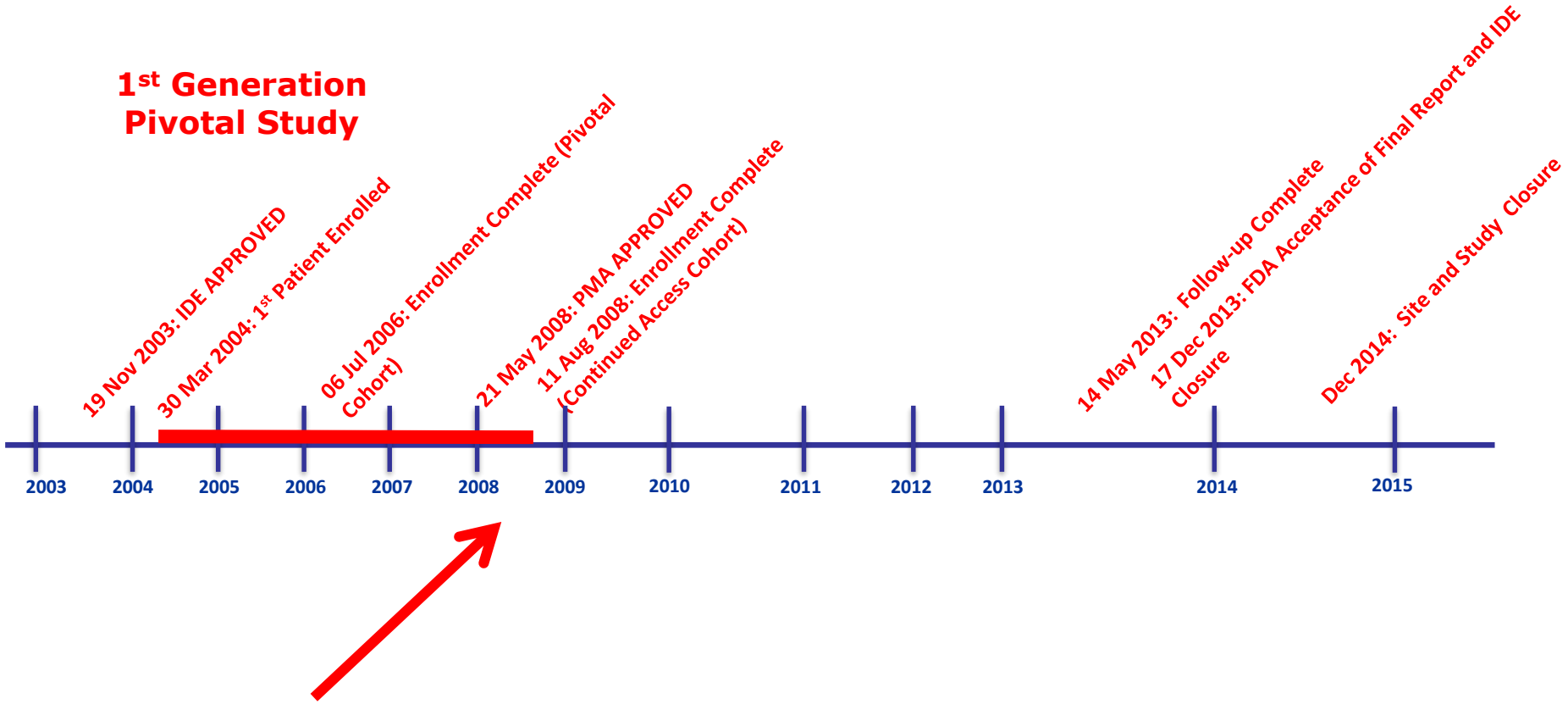
Presentation: Post-Market Studies: Large Investment, Little Return, CRT 2015, FDA Town Hall, Washington DC, February 24, 2015.

Thoracic Endovascular Graft

Indicated for endovascular treatment of patients with aneurysms/ulcers of the descending thoracic aorta having morphology suitable for endovascular repair

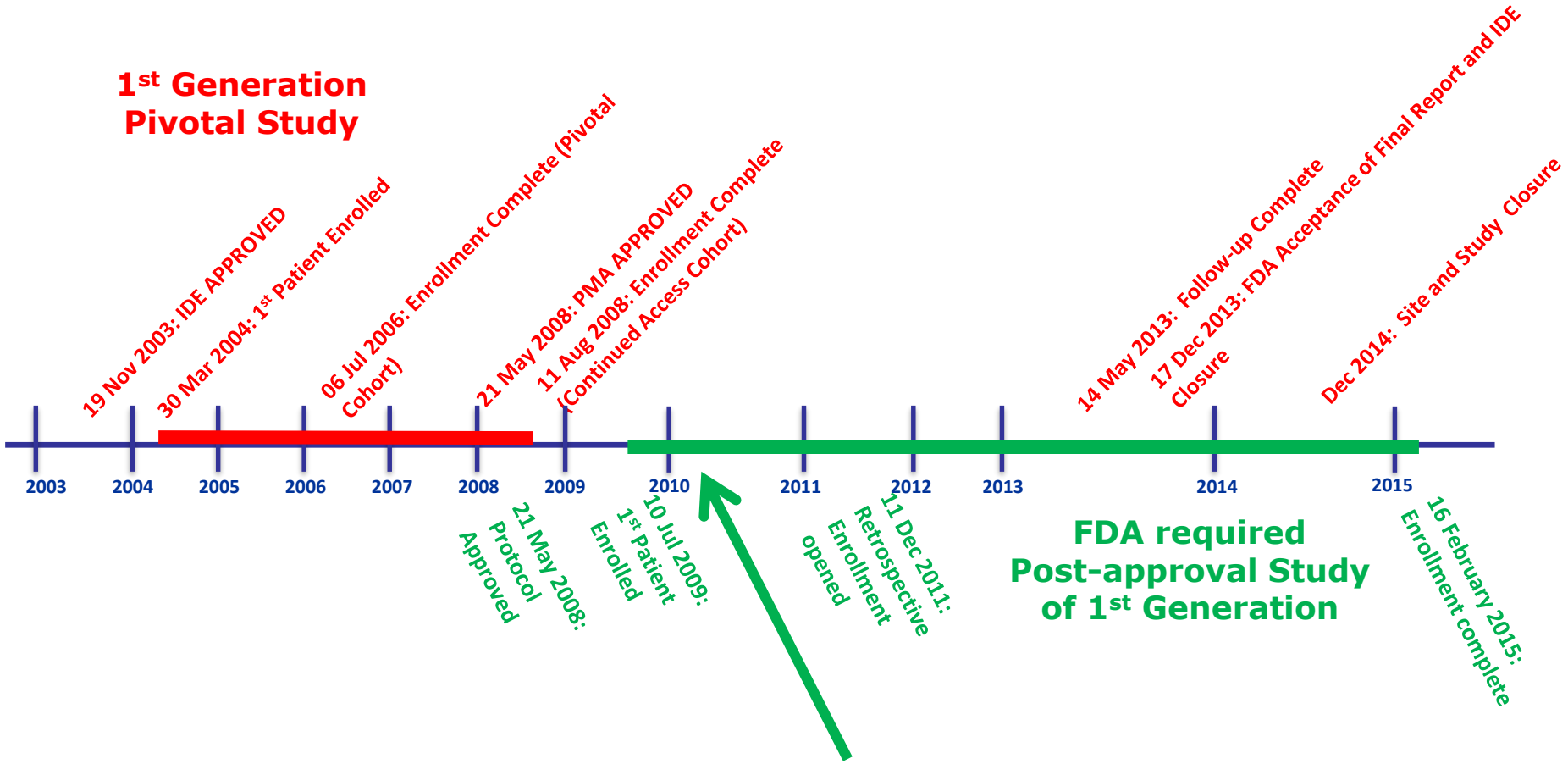
- Long history of use in Europe and Australia
- Gen 1 approved for use in the U.S. May 21, 2008
- U.S. approval required post market study (115 endovascular treatment patients and two substudies)
  - Per 21 CFR 814.82

Zenith® TX2 ® Pivotal Study - Traditional Path



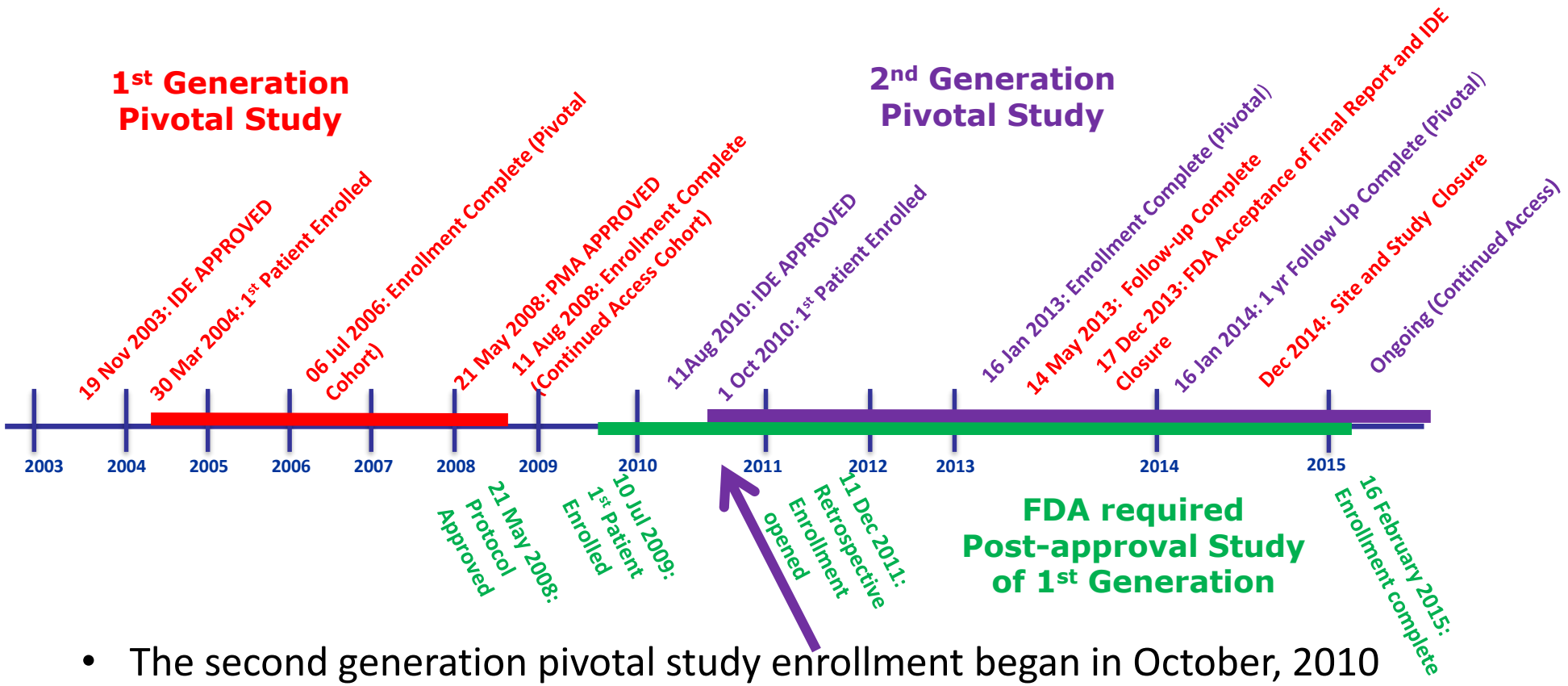
- The first generation pivotal study - U.S. regulatory approval on May 21, 2008.
- Enrollment period

Zenith® TX2 ® PAS as Condition of Approval - Traditional Path



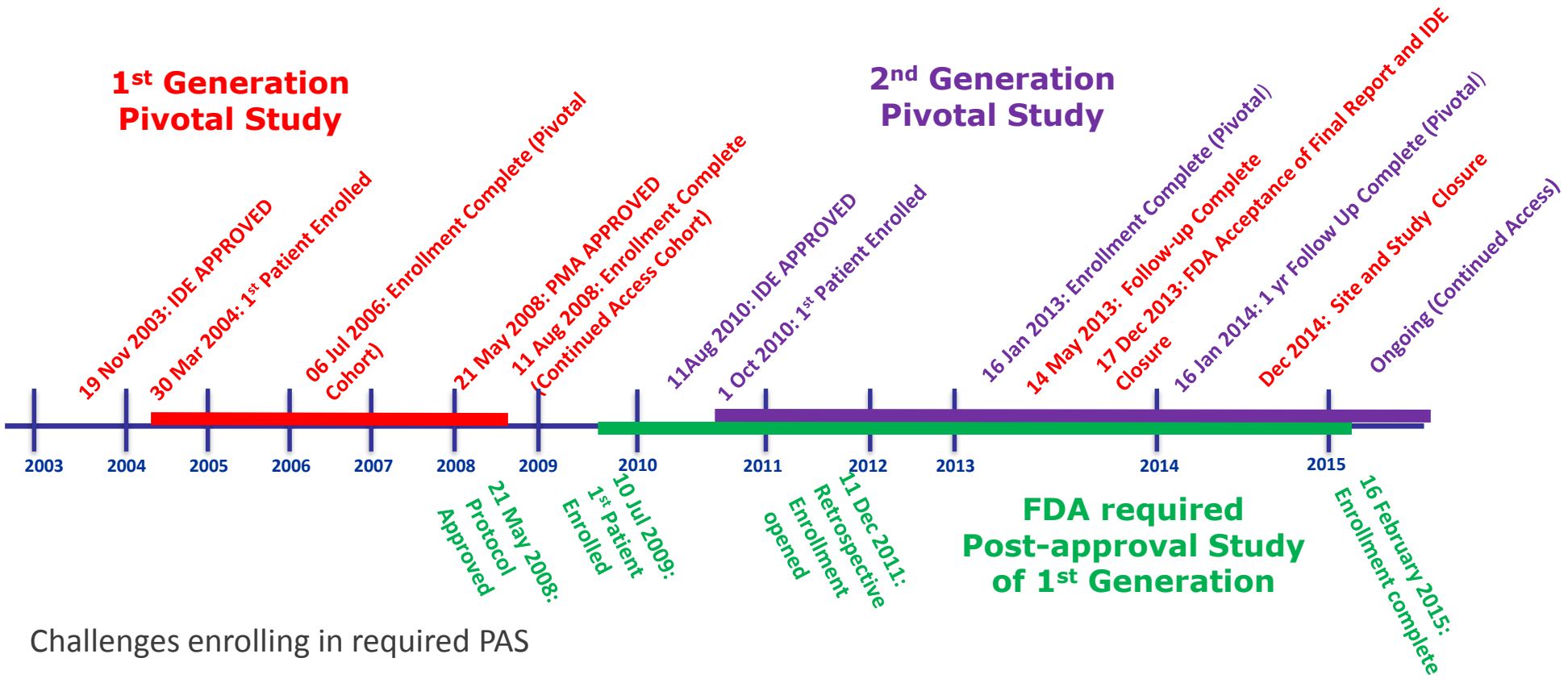
- 1st generation PAS – first patient enrolled on July 10, 2009
- Enrollment in PAS takes > 5 years to complete, even with huge effort

Zenith® TX2 ® Pivotal Study for Gen 2 – Traditional Path



- The second generation pivotal study enrollment began in October, 2010
- Enrollment for the 1st generation PAS and the 2nd generation pivotal overlap
- Enrollment period

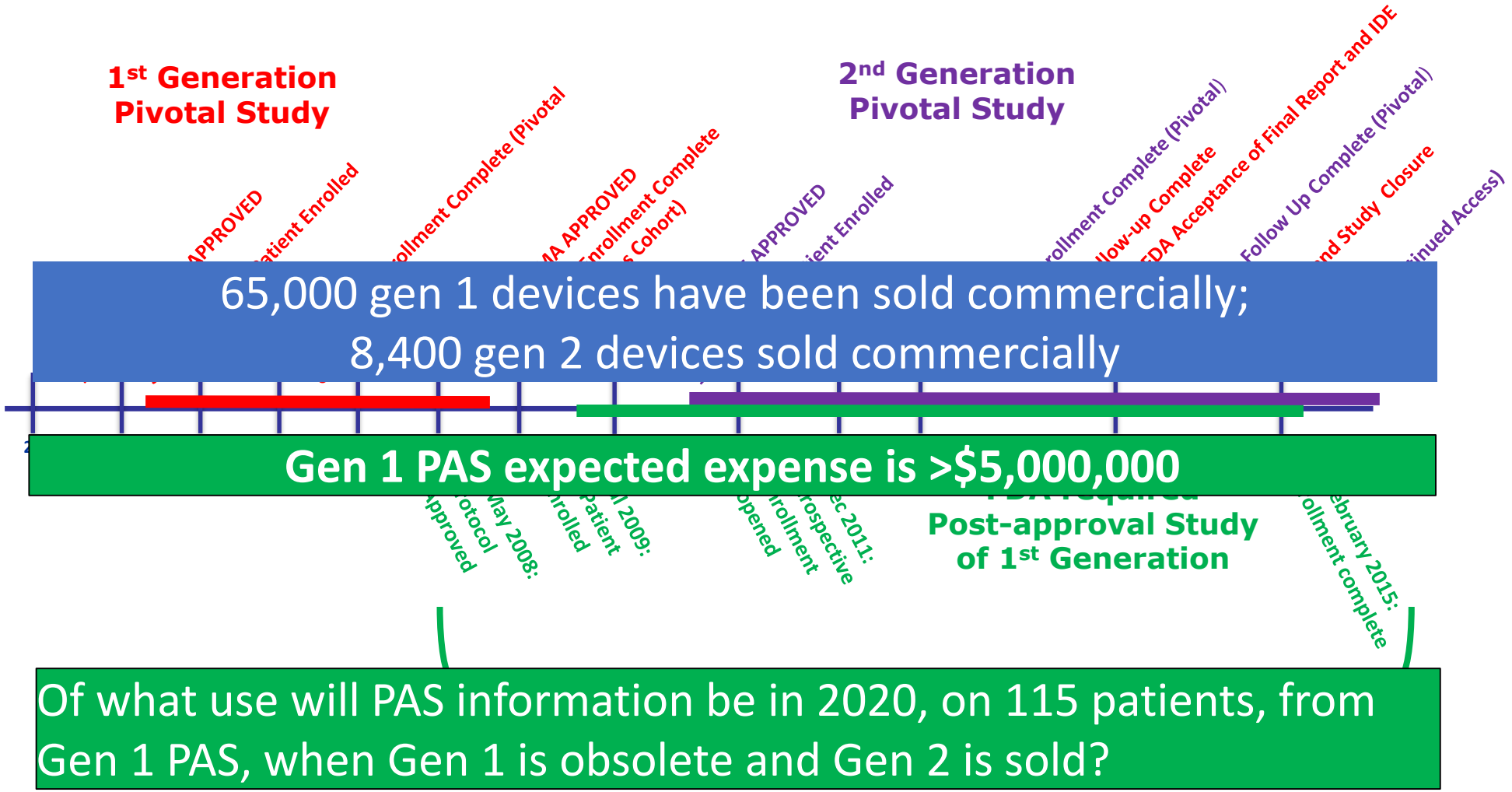
Challenges



Challenges enrolling in required PAS

- Encouraging a patient to enroll in the Gen 1 PAS when the Gen 2 study is enrolling
- Additional imaging obligation of Gen 1 PAS, when Gen 1 device is commercially available
- Encouraging hospitals and physicians to participate in a PAS, when interest lies in evaluating new, investigational Gen 2 products

Value question?



Large investment, little return when studies driven by requirements without consideration of practicality.

Limitations of traditional PAS

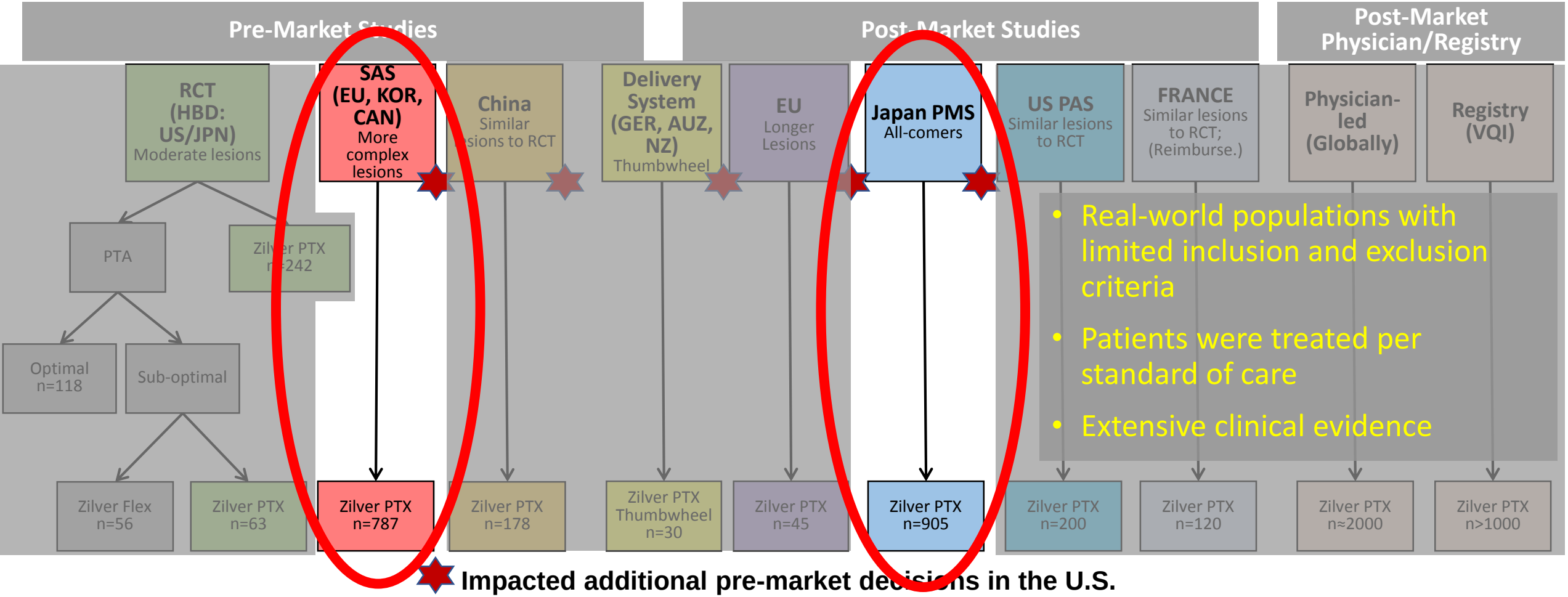
- Enrollment challenges: little motivation for physicians/patients
- Often long timelines, high cost
- Impractical generational overlap of clinical studies (pre/post-market)
- Not reflective of real world use (population/indication/physician)

RWE example: longer lesion indication

https://evtoday.com/pdfs/et1017_RU_FDA.pdf

- Zilver PTX longer lesion indication
- FDA/DCD/PIDB has considered RWE sufficient to support the approval of several recent regulatory submissions for both marketing approval and postmarket surveillance
  - Weighed the benefits and risks
  - RWE collection and analysis methods ensured relevance and reliability of the data
  - Using RWE was appropriate and least burdensome to support the reasonable assurance of safety and effectiveness
  - Developing a prospective analysis plan with prespecified success criteria is advantageous

RWE example: longer lesion indication



Impacted additional pre-market decisions in the U.S.
(additional indications, stent sizes, delivery system modification)

RWD

- The conversation is changing
  - As an alternative to a traditional PAS, can we extract data from the patients being treated commercially?
- RWD contains a patient population that typically includes all-comers, facilitating
  - More accurate reflection of real world use
  - A potential broader evaluation of available data on regulated products
- These data are “real-world” because patients are treated by numerous doctors outside of traditional closely controlled clinical studies, and potentially lacking oversight by clinical study monitors.
  - Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. (1)

Pursuing a RWE project

RWD → RWE

Real-World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD. (1)

How does data become evidence?

- Through an evaluation of quality, and data analysis

- Data collected under a pre-specified quality plan (i.e. GCP, ISO 14155, or other appropriate standard) is evidence
- Data analyzed under a pre-specified plan may also be evidence, depending on the quality of the data

- In practice, applications of RWD → RWE will include the concepts of a quality plan and an analysis plan, along with (or encapsulated within) a study design protocol

Principles of RWD/registry quality

- Quality is defined as conformance to requirements, not perfection
- The planned use of the data determines the requirements and therefore the relative importance of each element related to quality

→ Quality is about fitness for purpose and reliability of conclusions

Gliklich R, Dreyer N, Leavy M, eds. Registries for Evaluating Patient Outcomes: A User's Guide. Third edition. Two volumes. (Prepared by the Outcome DEcIDE Center [Outcome Sciences, Inc., a Quintiles company] under Contract No. 290 2005 00351 TO7.) AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014. http://www.effectivehealthcare.ahrq.gov/registries-guide-3.cfm, accessed May 11, 2016.

Quality challenges of RWE

- RWE is only as good as the RWD that supports it
- Stakeholders may not agreement on definition of “Quality”
  - Adequate quality to one is not adequate quality to another
- Over-specifying quality requirements increases burden on the system
  - With an increased burden, RWE has reduced economic value
- Under-specifying quality requirements may result in misleading evidence
- Data extraction and data integration

Other challenges include the topics of:

- Patient consent, patient privacy, IRB oversight, data ownership

FDA guidance on RWE

- 2017 Guidance: *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices* (1)

- Guidance contains many considerations for determining whether data is suitable evidence for regulatory decision making
  - Relevance
  - Reliability

- Many of the considerations are present in the process of, and deliverables from, GCP

- Ultimately, the guidance is about data quality, and study design

How to pursue a RWE project?

- Know your data
  - Understand the quality
  - Be comfortable with the limitations
- Know your product
  - Have a fundamental understanding of how it works, how it is used, and the patient population in which it is used
- Develop a plan
  - Data collection, data combining, data extraction, data analysis

→ Leads to reliable inference and evidence

Overall development

Borrowing from ICH principles

- Context – should describe the overall plan, which could include
  - Any exploratory assessments of the RWD
  - What would be expected from a confirmatory analysis
- Scope
  - Population representation/selection
    - How they are being extracted from the RWD?
    - Treatment exposure
    - Selection criteria will still be needed
  - Variable definitions - inconsistent across various sources of RWD
- Avoiding Bias
  - Perform an assessment of selection bias (at the dataset level, and patient level)
  - How does the RWD avoid bias in its generation?
  - How will the statistician avoid bias in the analysis?

Design and conduct considerations

- Design Configuration
  - Patient matching, performance goal, pragmatic trial
  - Performance characterization
- Adequacy of evidence - what will indicate a successful result?
  - Significant and/or clinically relevant treatment effect
  - Covariate adjusted treatment effect
  - Propensity score adjusted treatment effect
  - Correlation
  - Performance data
- Sample Size - n="all", n="half", or something else?
- Interim Analysis
  - How much follow-up is enough? Might you wait for more data to accumulate?
- Changes in selection criteria

Statistical inference

- Valid statistical inference comes about through proper study design
  - Whether designing a prospective RCT, or extracting and combining data from multiple sources of RWD
- Methodological assumptions must be satisfied, or reasonably justified
  - Example: Fisher's Exact Test
    - Dichotomous measurement
    - A directional hypothesis is assumed - positive or negative association, but not both
    - The population is representative
    - Independence of samples: the value of each sampled unit is not affected by the value of the other sampled units
    - Mutual exclusivity: the given case should fall in only one cell in the table
    - The sample is drawn from a population based on a process of random sampling

	Test	Control
Pass	% n/N	% n/N
Fail	% n/N	% n/N

Independence and mutual exclusivity – harder than you think

- Physicians will follow a course of treatment over time
- Patients may be treated with multiple comparable treatments
  - At the same procedure, or a different one
- In some cases, it may be difficult to determine which procedure is “index”
- May be difficult to identify the same patient across multiple sources of RWD

Important additional considerations

- Identifying, and excluding, prior use data
  - Is your pivotal study data contained in the RWD?
- Suppose you get it wrong?
  - Mechanism for additional analyses of the data
- Some findings may require a confirmatory study
- Attribution of adverse events in procedure where multiple devices are used
- Incorporation of device design and usage information

Device design considerations

- Device design parameters (e.g., radial force, flexibility) are established to target a specific patient population
  - A type of selection bias
- Example: in peripheral vascular disease, physicians tend to use different devices for different types of patients:
  - Supera® Stent (Abbott Vascular) in heavily calcified lesions
  - Viabahn® (Gore®) in long calcified total occlusions
  - Zilver® PTX® (Cook) in patients that have failed previous therapy
  - Drug coated balloons in simple lesions
- It is important to understand the impact of these different uses on the expected clinical outcomes

Data analysis considerations

- Prespecify the analysis
  - Methods to confirm assumptions
- Analysis datasets
  - A test dataset may be beneficial
  - The final dataset should exclude the test dataset
- Missing values and outliers (complex clinical cases)
  - RWD will have more of these
  - Missing data unlikely to be MAR
- Estimation, confidence intervals and hypothesis testing
  - Emperical distribution development to ascertain the possible range of treatment effect
- Adjustment of significance and confidence levels
- Subgroups, interactions, covariates, unidentified confounders

Additional discussion topics

Or, points to ponder

Additional points to ponder

- How can we ensure RWE provides adequate information to manufacturers and regulators for:
  - Global regulatory reporting
  - Moral and legal responsibilities (e.g. risk management, safety signals)
  - Product/technique improvement
  - Physician and patient education
- Access is often only to aggregate dataset; limited information
- Will use of RWE be more efficient than traditional clinical trials?
  - Cost for and control of access to the RWD/RWE

Additional points to ponder

- Will regulators accept RWE as adequate to support approvals and fulfill post-market requirements
  - EHR as potential source data
  - Limited data elements (is an important covariate missing?)
  - Limited monitoring or ability for BIMO
  - Limited imaging
  - Informed consenting questions
  - Broad patient population
    - “strict on label” versus “near label”
  - Can RWE be used to support approval of first of a kind devices?

Thank you!

References

1) Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices; Guidance for Industry and Food and Drug Administration Staff; August 31, 2017.
2) ICH E9, Statistical Principles for Clinical Trials, 1998

Contact

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