



# Post- Approval Studies Program Update

**Danica Marinac-Dabic, MD, PhD**  
**Director, Division of Epidemiology**  
**General and Plastic Surgery Devices Panel**  
**August 30, 2011**

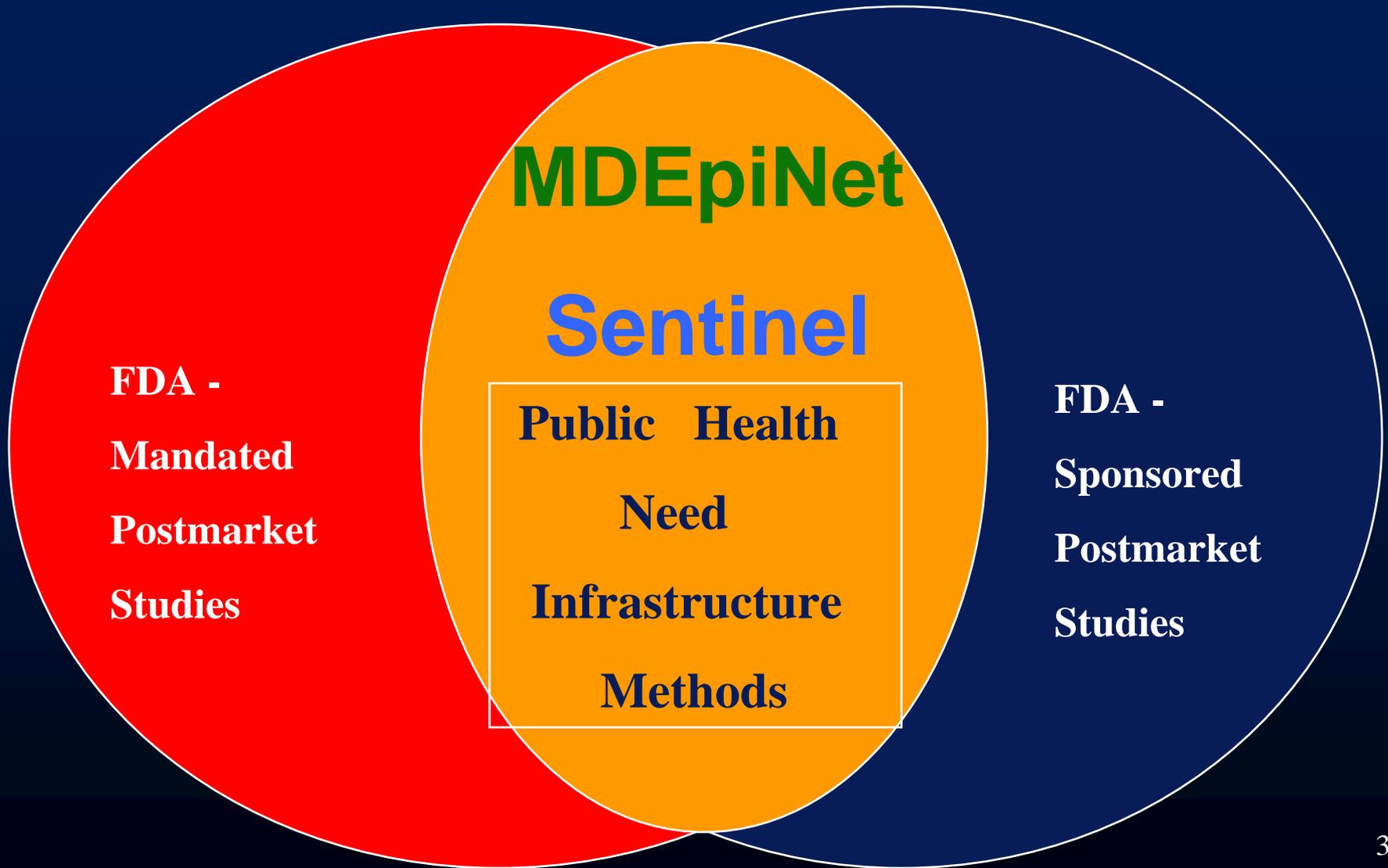


# Post-Approval Studies: Legal Authority

## 21 C.F.R. § 814.82

- **FDA may impose post-approval requirements at the time of approval of the PMA or by regulation subsequent to approval and may include:**
  - (2) Continuing evaluation and reporting on the safety, effectiveness, and reliability of the device for its intended use. FDA will state the reason and the number of patients to be evaluated.
  - (9) Other requirements as FDA determines necessary to provide (continued) reasonable assurance of the safety and effectiveness of the device.

# CDRH Postmarket Science



# PAS Program Highlights

- 2005 Established integrated CDRH PAS program
- 2005 Began raising scientific rigor of PAS
- 2006 Developed and instituted PAS tracking system
- 2006 Issued PAS Guidance
- 2007 Created PAS public website
- 2007 Instituted Advisory Panel updates
- 2008 Initiated BIMO inspections of PAS
- 2008 Focus on infrastructure building
- 2009 Focus on methods development
- 2010 Focus on strategic partnerships (e.g. MDEpiNet)
- 2011 Focus on strategic partnerships (e.g. ICOR)



# PAS Transparency Initiative

## Expanded PAS Webpage- December 20, 2010

Ongoing Studies	Completed Studies
<p>Detailed Study Protocol Descriptions:</p> <ul style="list-style-type: none"> <li>Study Population</li> <li>Sample Size (sites and patients)</li> <li>Study Endpoints</li> <li>Data Collection and Follow-up Visits</li> </ul>	<p>Detailed Study Protocol Descriptions:</p> <ul style="list-style-type: none"> <li>Study Population</li> <li>Sample Size (sites and patients)</li> <li>Study Endpoints</li> <li>Data Collection and Follow-up Visits</li> </ul>
	<p>Final Data Summary:</p> <ul style="list-style-type: none"> <li>Number of Sites and Enrolled Patients</li> <li>Study Final Results</li> <li>Study Strengths and Limitations</li> <li>Recommended Labeling Changes</li> </ul>

<http://www.fda.gov/devicepostapprovalstudies>



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## Post Approval Studies

- The new Center for Devices and Radiological Health (CDRH) Post-Approval Studies Program encompasses design, tracking, oversight, and review responsibilities for studies mandated as a condition of approval of a premarket approval (PMA) application. The program helps ensure that well-designed post-approval studies (PAS) are conducted effectively and efficiently and in the least burdensome manner.
- On January 1, 2005, the oversight responsibility was transferred to CDRH's Office of Surveillance and Biometrics (OSB) and the PAS review functions were integrated into the medical device epidemiology program. Guidance on report format and content was developed to ensure optimal PAS reporting and review. <http://www.fda.gov/cdrh/osb/guidance/1561.html>.
- CDRH has established a new automated tracking system that efficiently identifies the reporting status of active PAS studies ordered since January 1, 2005. This system represents CDRH's effort to ensure that all PAS commitments are fulfilled in a timely manner. The effective tracking system is based on study timelines incorporated in study protocols and agreed upon by the CDRH and manufacturer.
- In addition to this internal tracking system, CDRH launched this publicly available webpage to keep all stakeholders informed of their progress. It displays not only the report status, but also study status (based on protocol-driven timelines) of each PAS.

A B C D E M O P S T U V W Z

63 records

[Show All Studies](#)

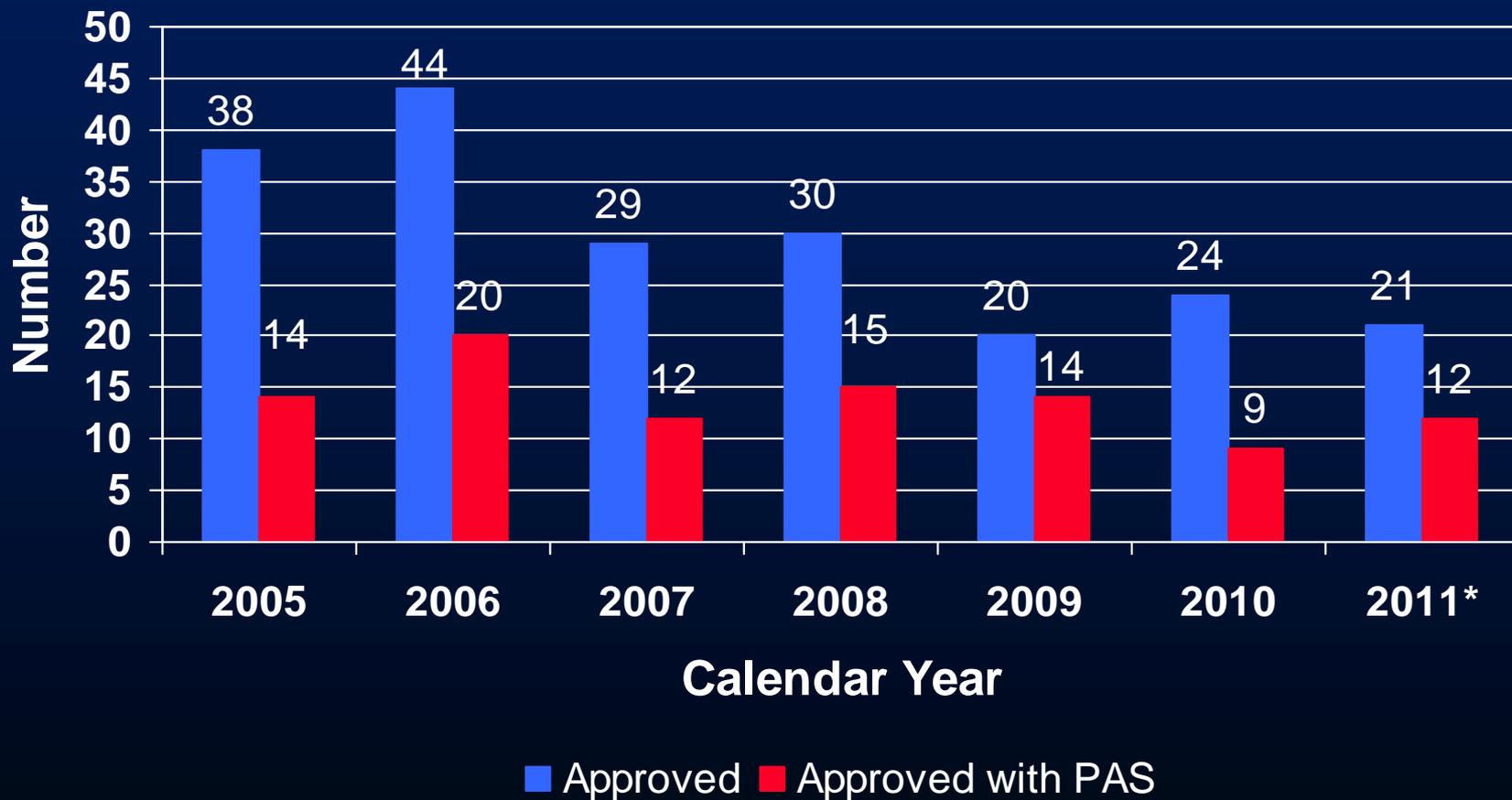
[Export to Excel](#) | [F.A.Q.](#) | [Guidance Docu](#)

Application Number	Applicant Name	Device Name	Medical Specialty	Date PMA Approved	Post-Approval Study Commitment	Study Name	Protocol Approved	Study Population	Stu Sta
<a href="#">P040038</a>	ABBOTT VASCULAR DEVICES	XACT CAROTID STENT SYSTEM	Cardiovascular	09/06/2005	1. YOU HAVE AGREED TO CONDUCT THE FOLLOWING STUDIES AND TO REPORT ON THESE STUDIES EVERY <input type="checkbox"/>	<a href="#">PROTECT Study</a>	02/05/2007	Transitional Adolescent B: 18-21 yrs, Adult: >21	Stud time
						<a href="#">EXACT Study</a>	10/12/2005	Transitional Adolescent B: 18-21 yrs, Adult: >21	Stud time
<a href="#">H040006</a>	ABIOMED, INC.	ABIOCOR	Cardiovascular	09/05/2006		<a href="#">Abiocr Artificial Heart</a>	09/05/2006	Transitional Adolescent B: 18-21 yrs, Adult: >21	Stud time

# Overall PAS Update



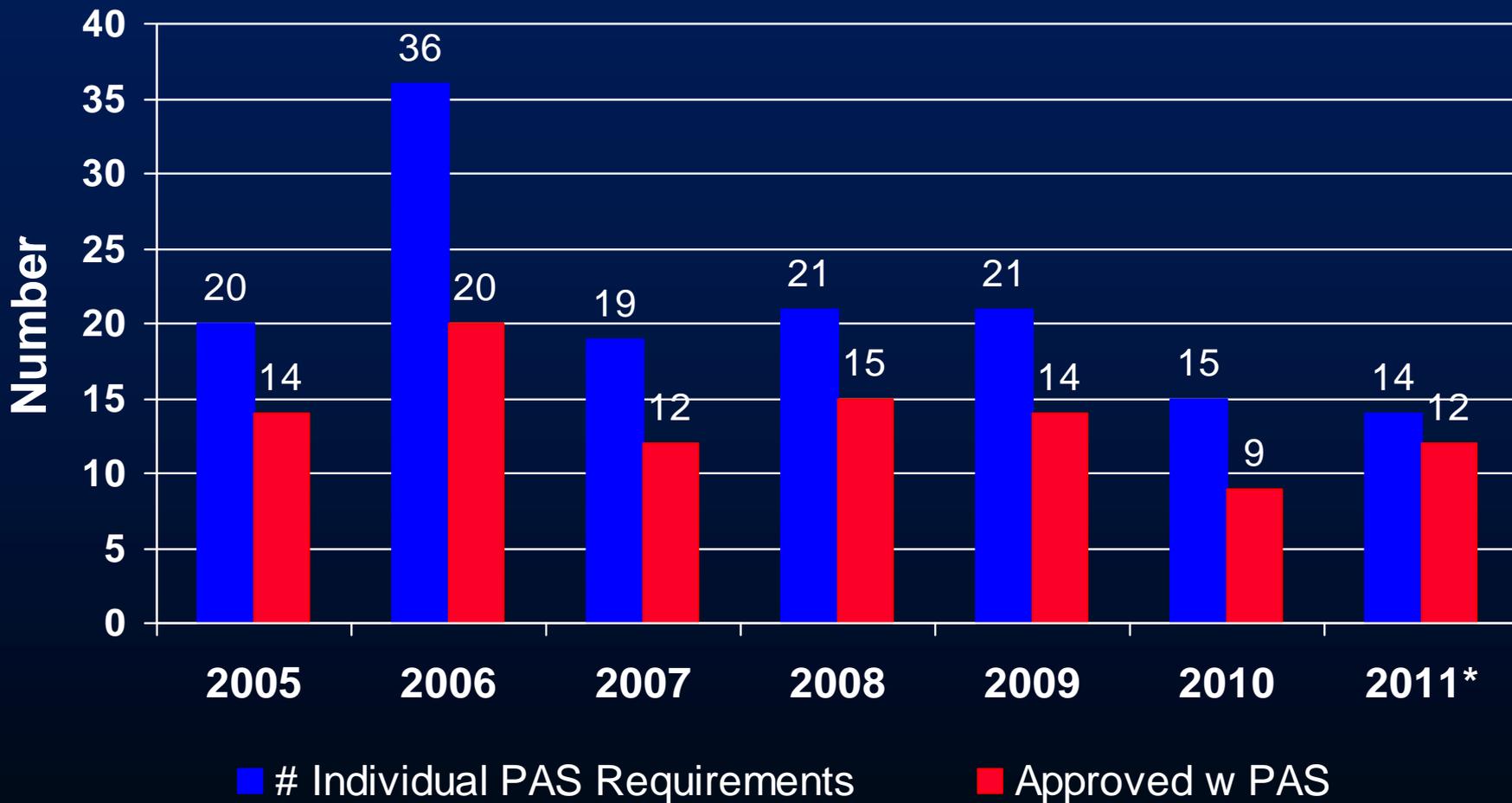
# Number of Approved Original PMAs and Panel-Track Supplements (PTS), 2005-Present



\*As of 8/15/2011



# Number of Original PMAs and PTS Approved with PAS Order and Number of Individual Requirements, 2005 to Present

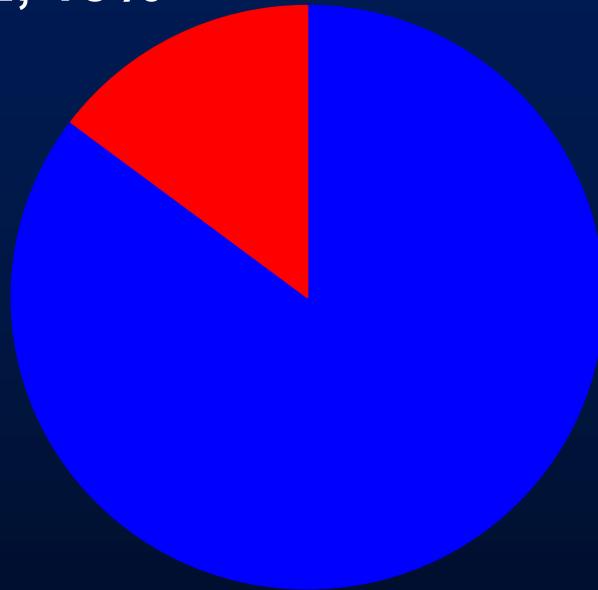


\*As of 8/15/2011



# Compliance for All PAS Requirements, N=351\*

52, 15%



299, 85%

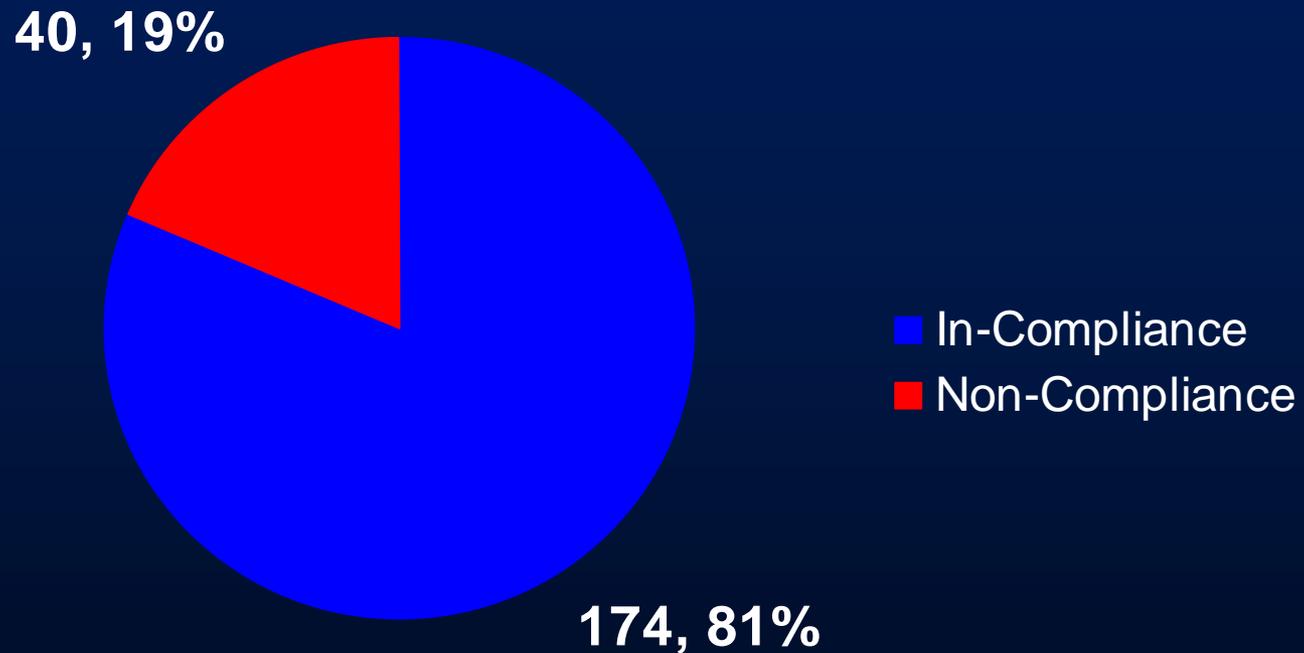
- In-Compliance
- Non-Compliance

As of 8/15/2011

\* includes completed studies



# Compliance with PAS Requirements 2005 to Present, N=214

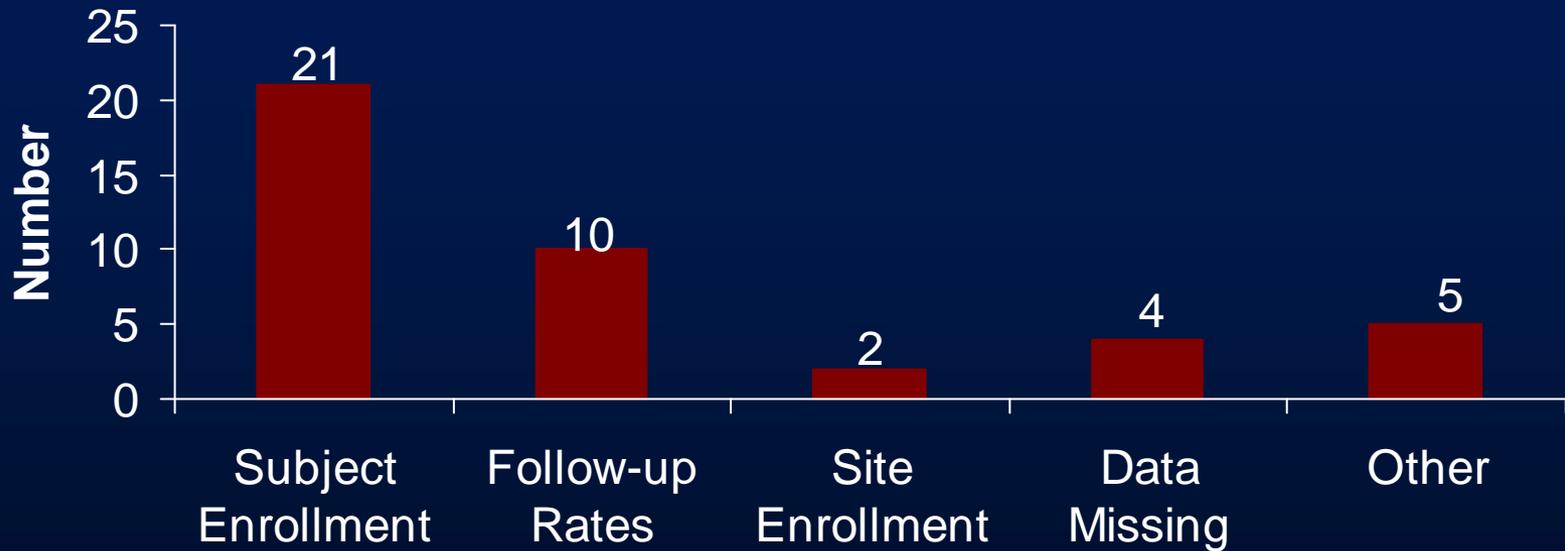


As of 8/15/2011

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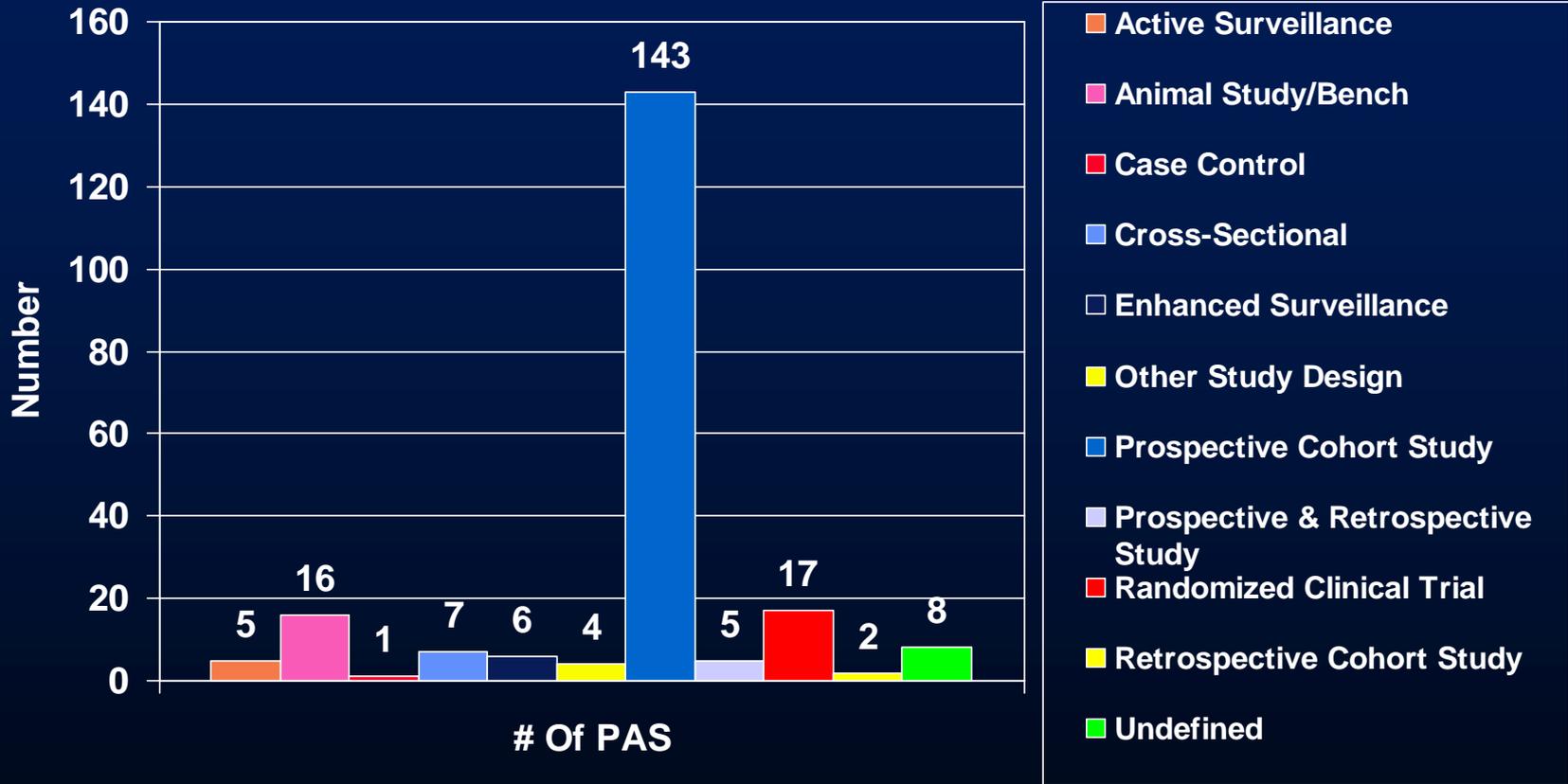
# Reasons for “Progress Inadequate”, N=42



As of 8/29/11



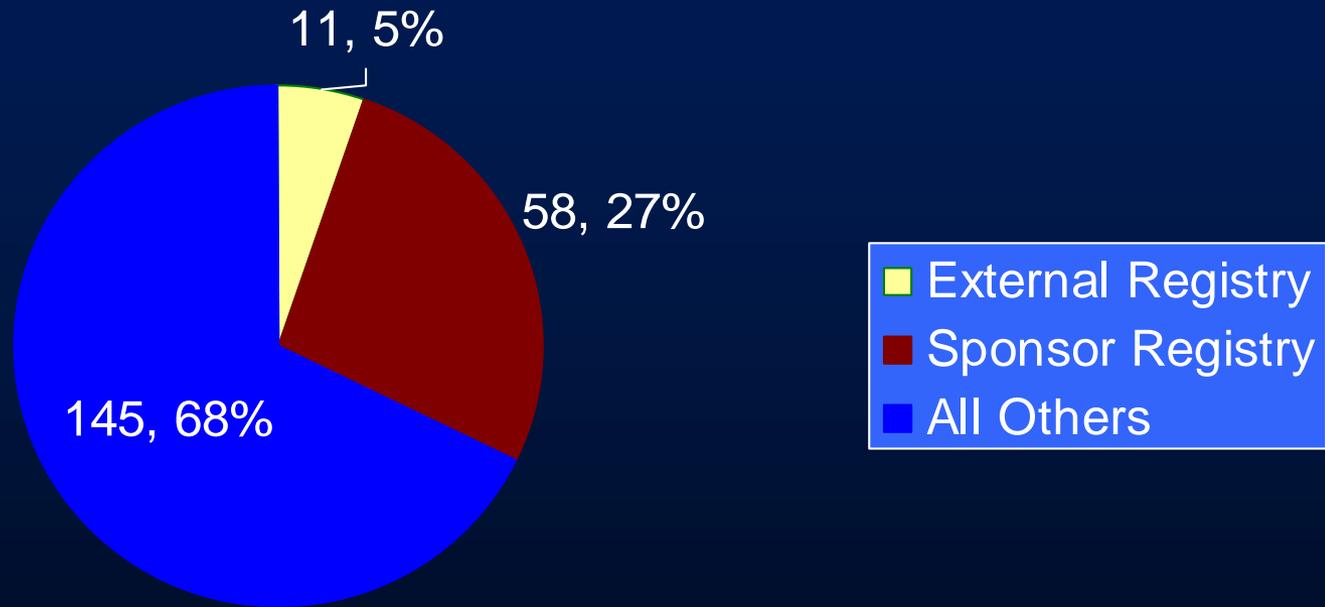
# Study Designs for PAS



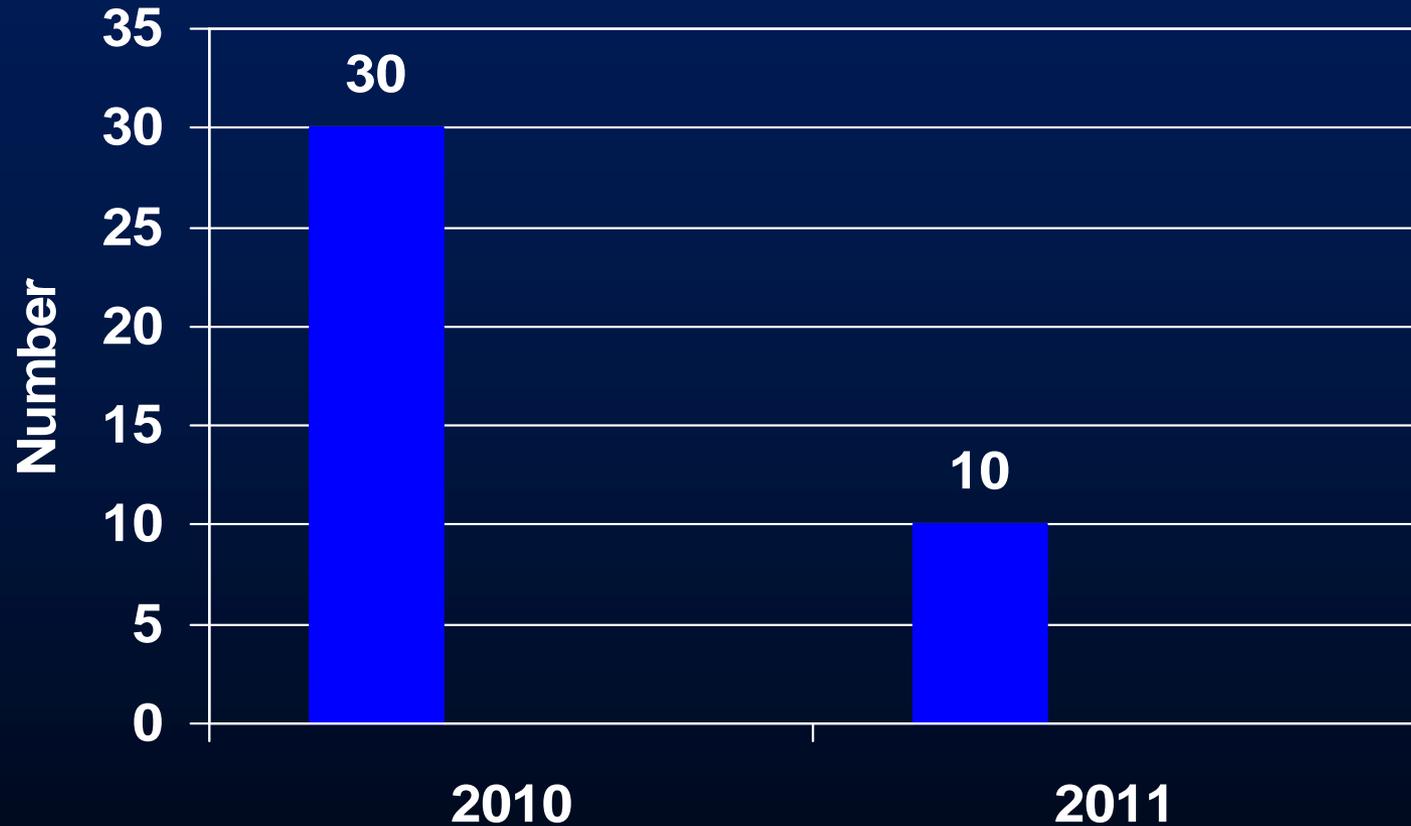
N=214



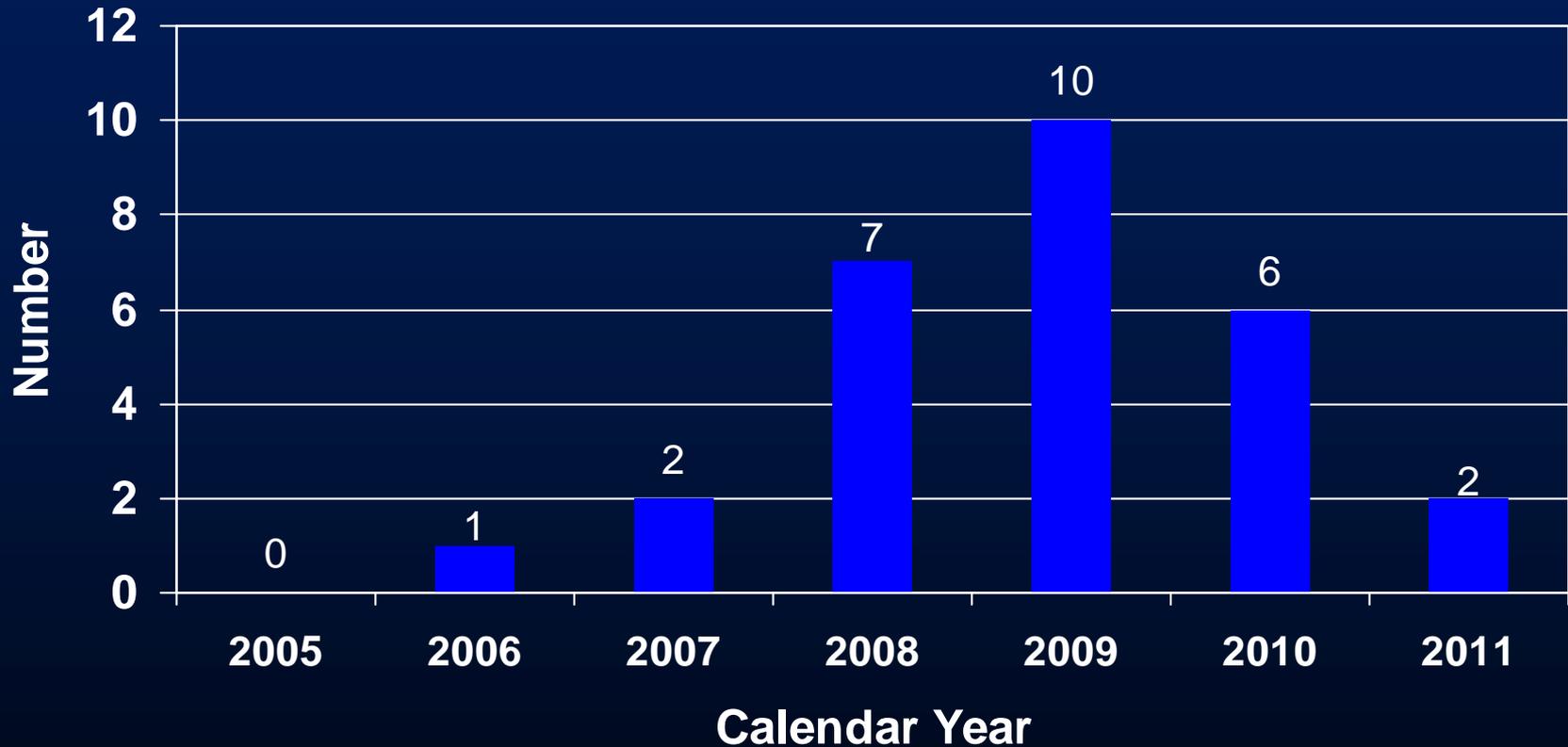
# PAS Data Sources



# Final PAS Results Posted on the Web



# Labeling Change Requests Based on PAS Final Results



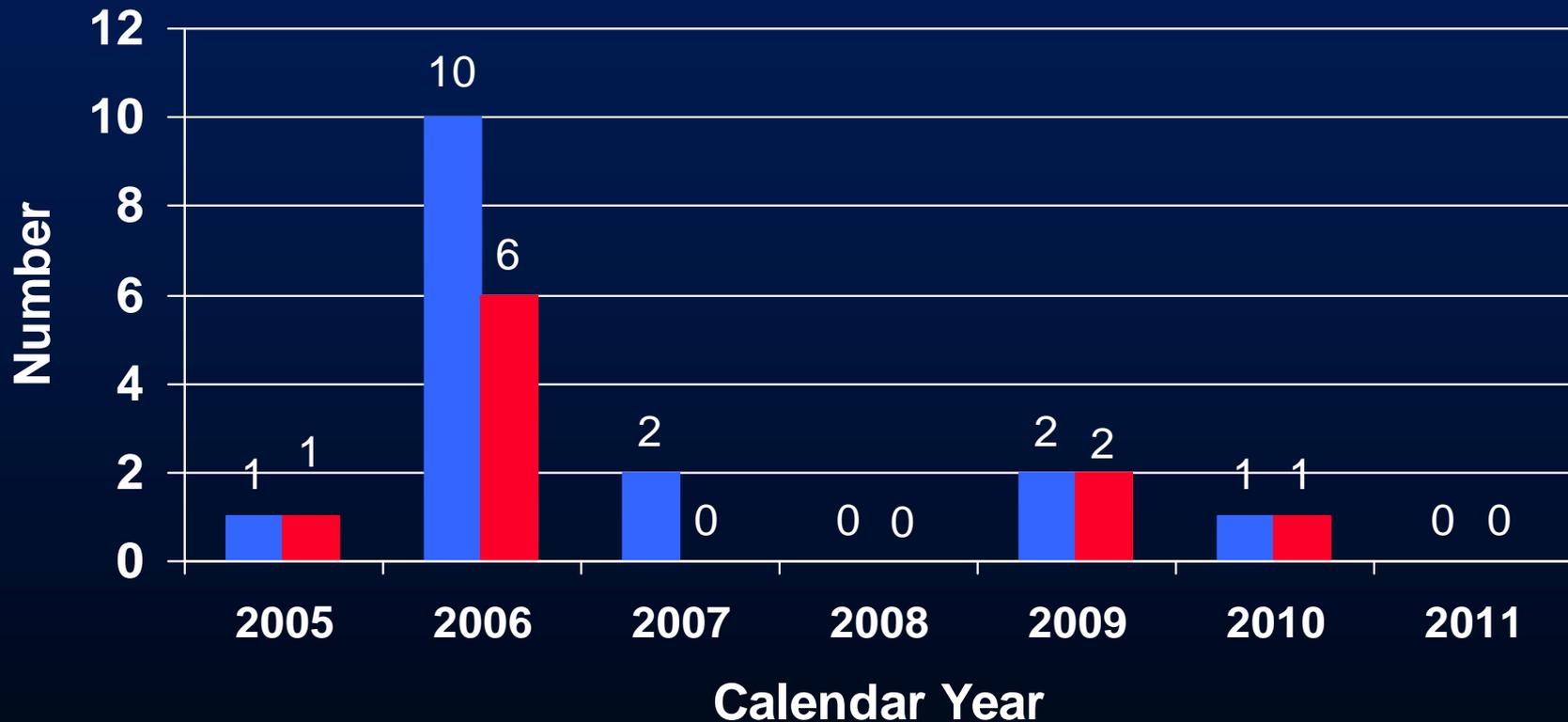
As of August 15, 2011



# PAS for General and Plastic Surgery



# Number of Approved Original PMAs and PTS General and Plastic Surgery

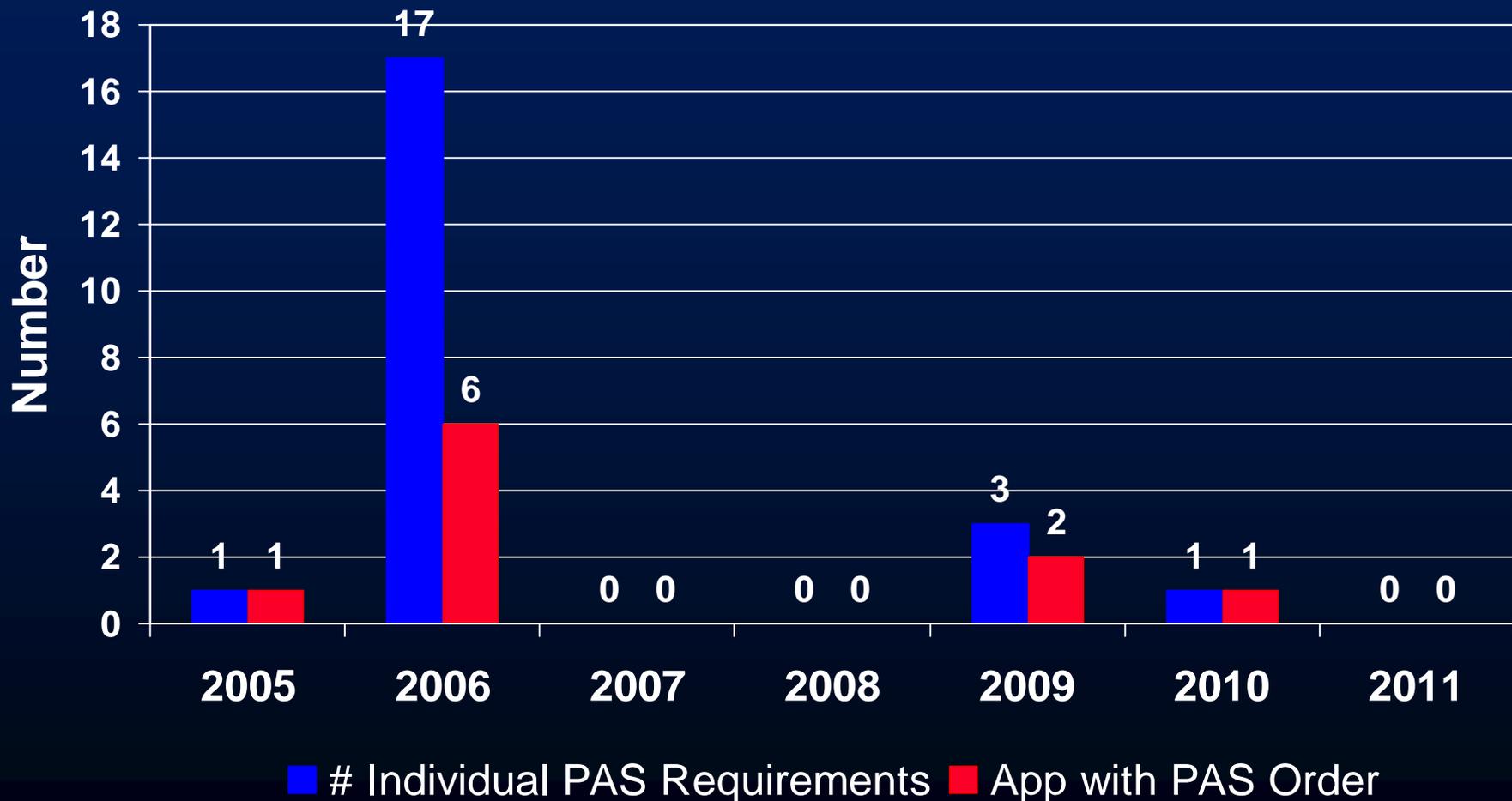


As of 8/15/2011

■ Approved ■ Approved with PAS



# Number of Original PMAs and PTS Approved with PAS Order and Number of Individual Requirements, 2005 to Present General and Plastic Surgery



As of 8/15/2011

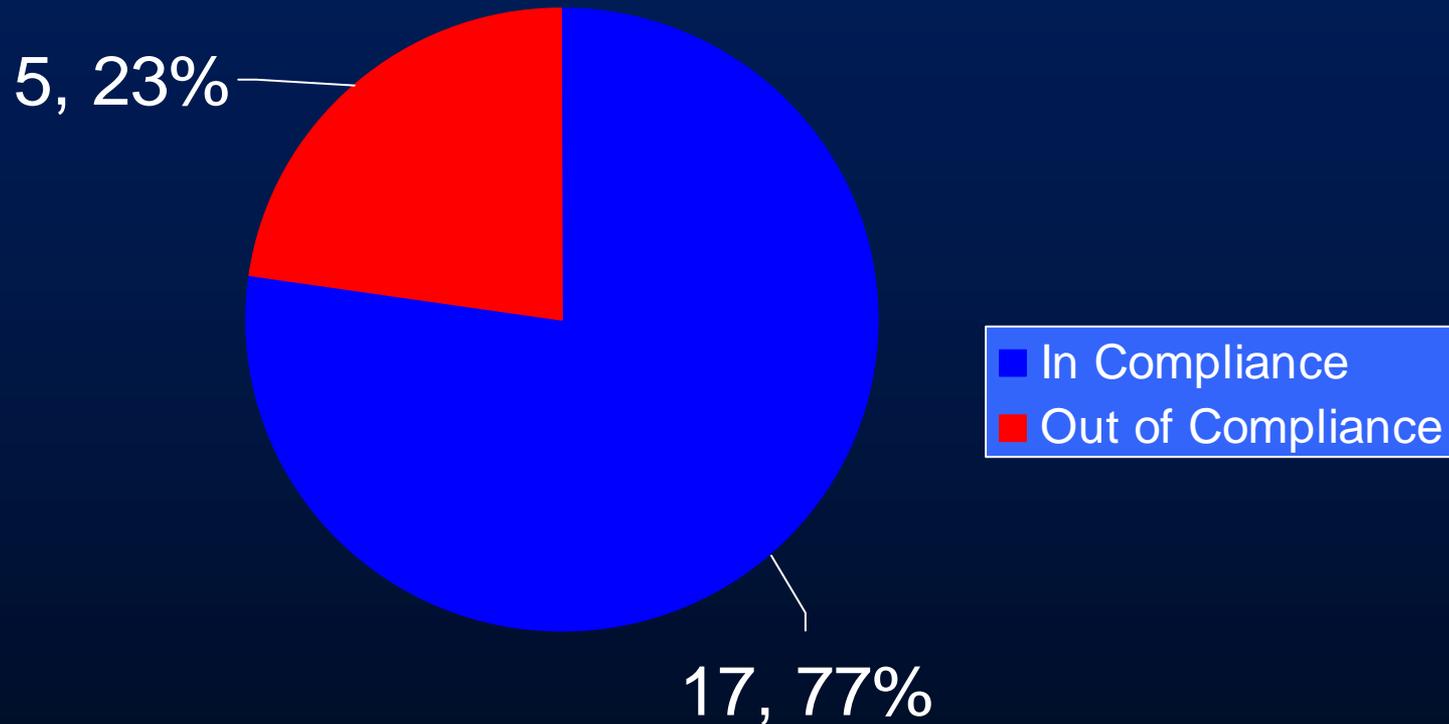
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Division of Epidemiology

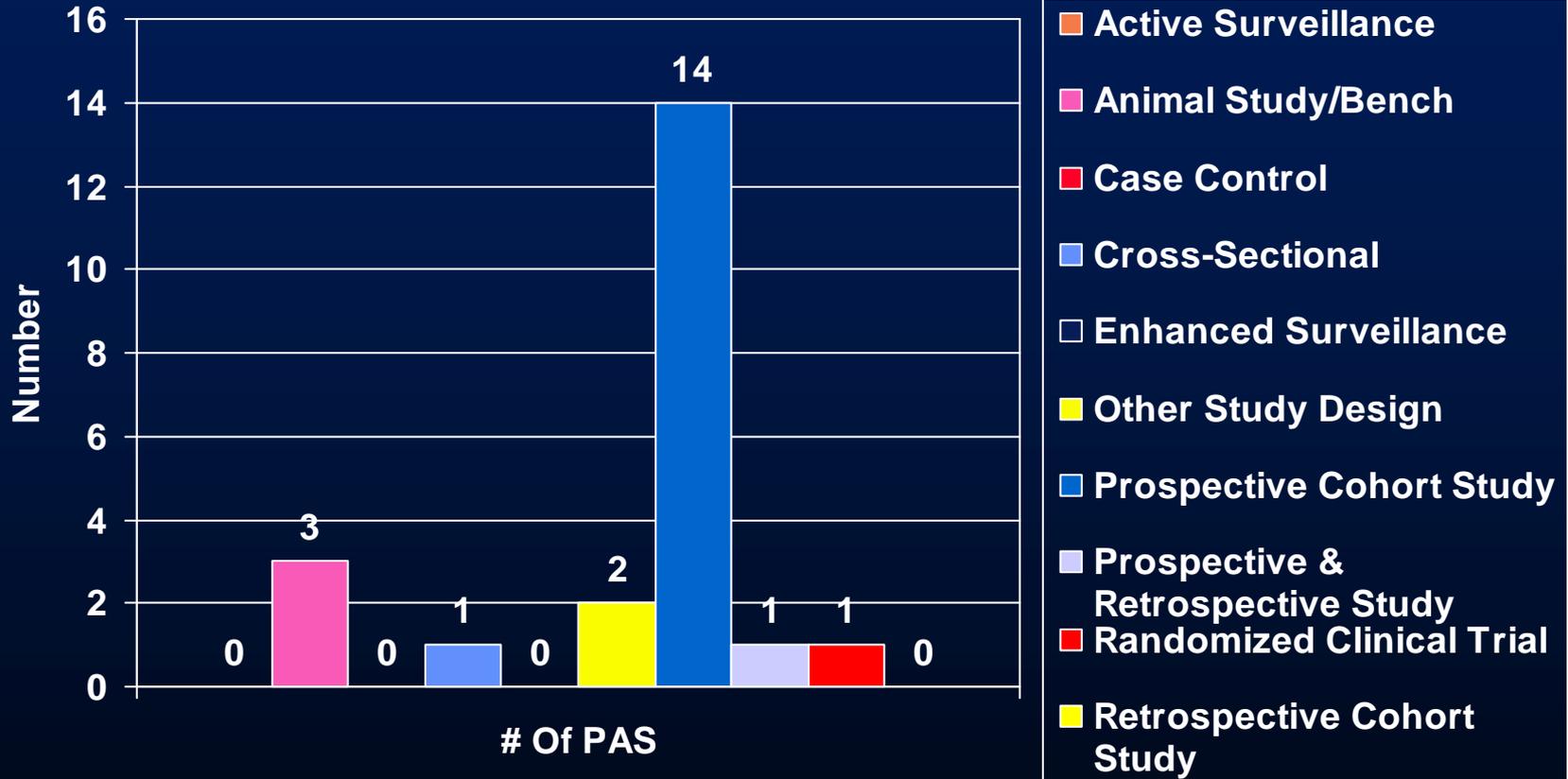


# Compliance with PAS Requirements General and Plastic Surgery – 2005 –present N=22

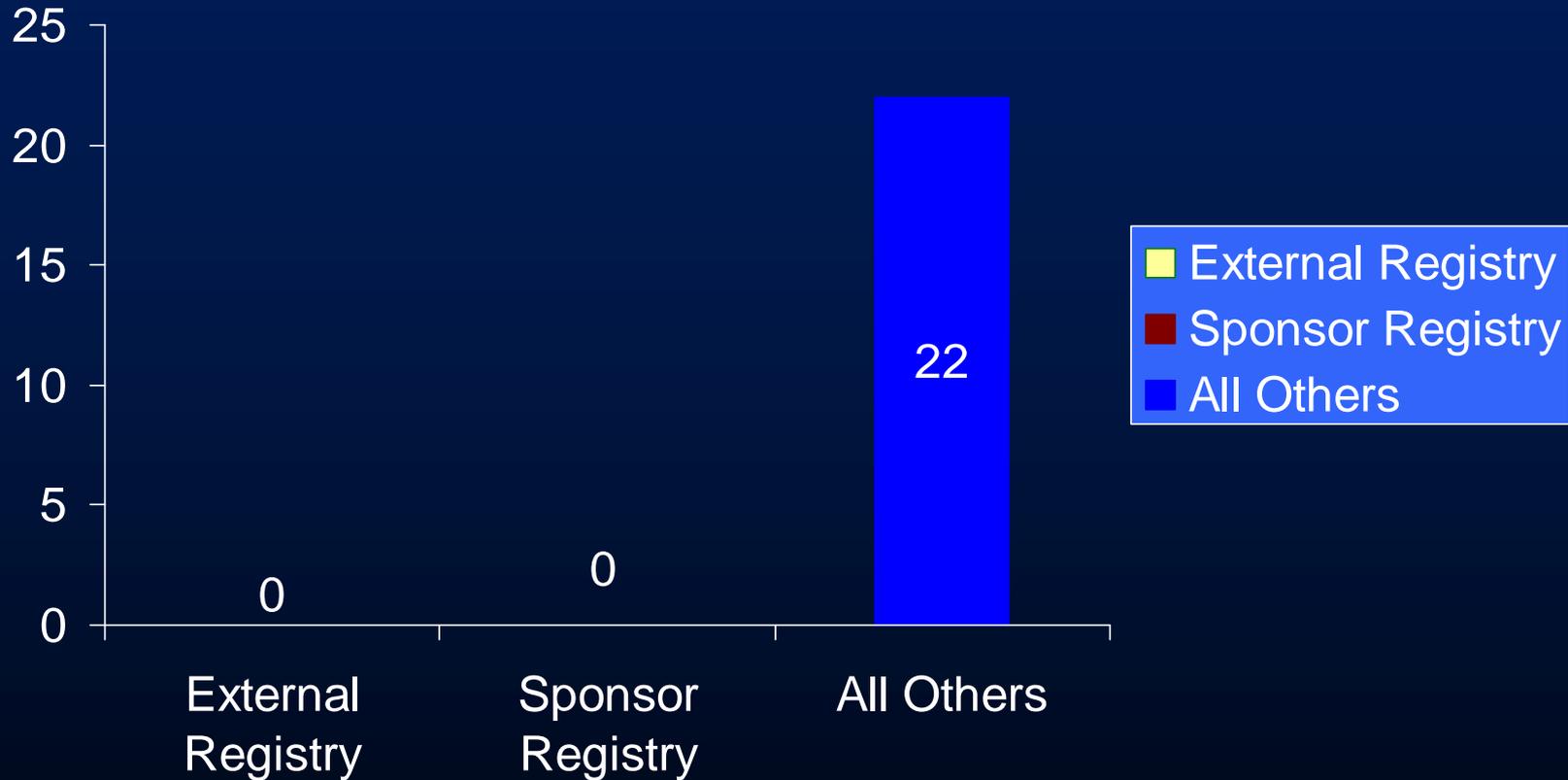


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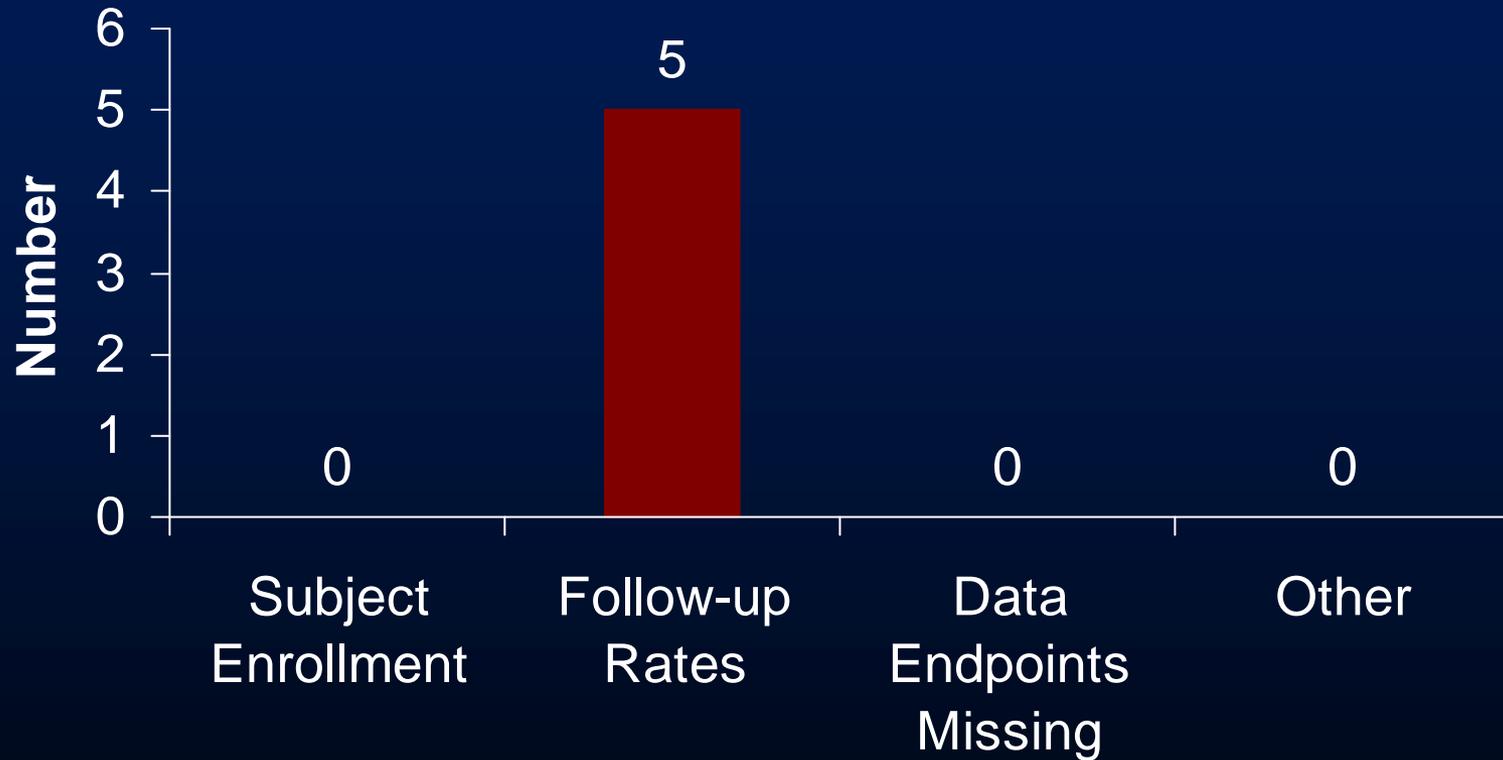
# Study Designs for General/Plastic Surgery



# PAS Data Sources: General/Plastic Surgery



# Reasons for “Progress Inadequate” General/Plastic Surgery PAS post-2005 N=5



As of 8/15/11



# Focus on Infrastructure



# CDRH Ongoing Registry Efforts

- **Use existing registries for PAS studies and surveillance**
  - ✓ INTERMACS (NIH, CMS, FDA)
  - ✓ Total Joint Replacement Registry (Kaiser)
  - ✓ Australian National Joint Replacement Registry
- **Facilitate new registry development**
  - ✓ Atrial Fibrillation Registry (ACC, HRS, STS)
  - ✓ American Joint Replacement Registry (AAOS)
  - ✓ Diagnostic and Therapeutic Bronchoscopy Registry (ACCP)
  - ✓ Uro-Gynecological Mesh Registry (U Mass)
  - ✓ IMPACT Registry (ACC)

# CDRH Ongoing Registry Efforts (cont)

- **Use existing registries for discretionary studies**
  - ✓ ICD Registry (ACC-NCDR)
  - ✓ Adult Cardio-Thoracic Database (STS)
  - ✓ Total Joint Replacement Registry (Kaiser)
  - ✓ Hospital for Special Surgeries Registry (Cornell)
  - ✓ OUS Orthopedic Registries (Australia, Denmark)
- **Explore registry capabilities**
  - ✓ Active surveillance: short-term and longitudinal
  - ✓ Linkages studies with Medicare claims data
- **Advocate for registries (AHRQ's Guide on Registries)**
- **Build methodological infrastructure for registries (ICOR)**

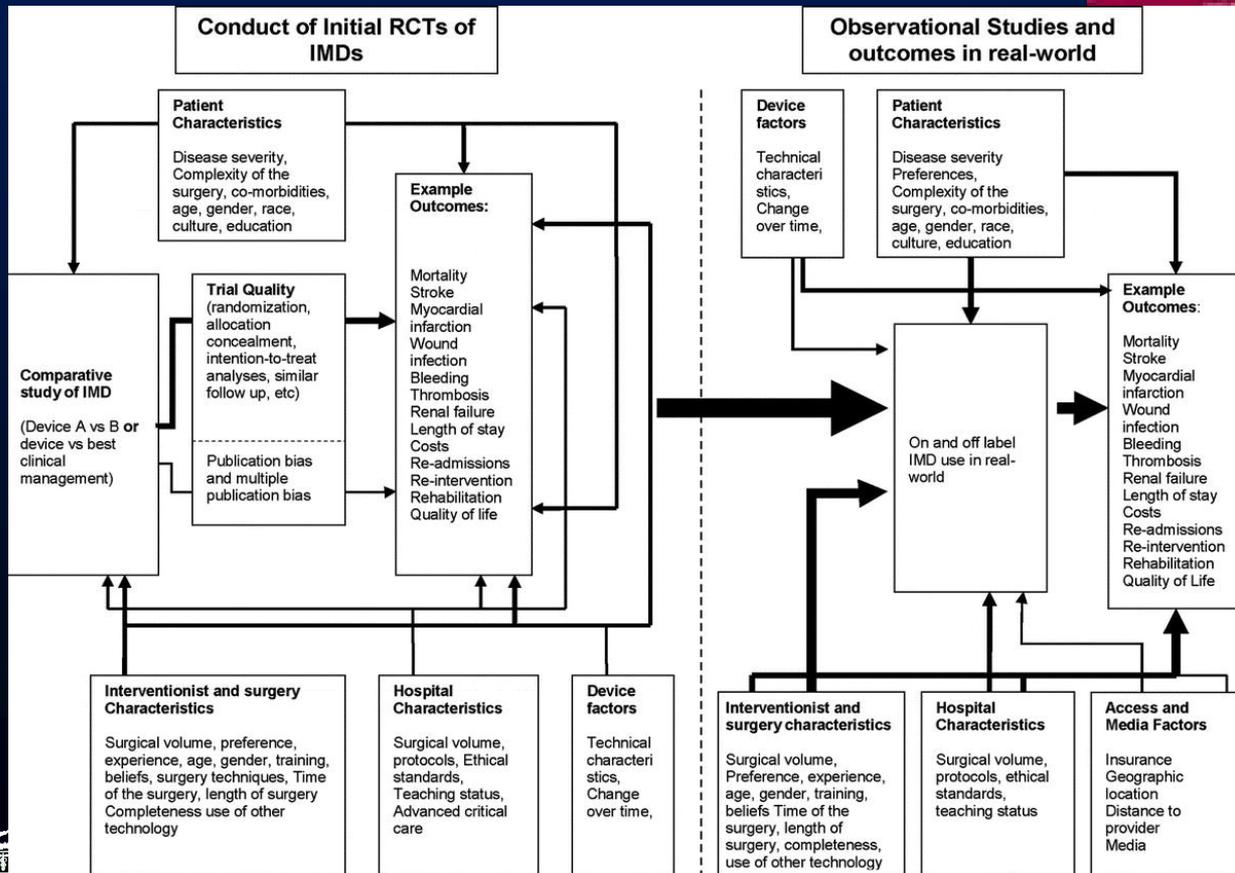
26



# Focus on Methods



# The framework for evidence appraisal for medical devices



Sedrakyan A, Normand, SL  
 Marinac-Dabic, D. et al. A  
 framework for evidence  
 evaluation in implantable  
 device studies. *Med Care* 2010



# Innovative Methods

Make better use of existing pre & post approval data

Integrate/combine when appropriate!

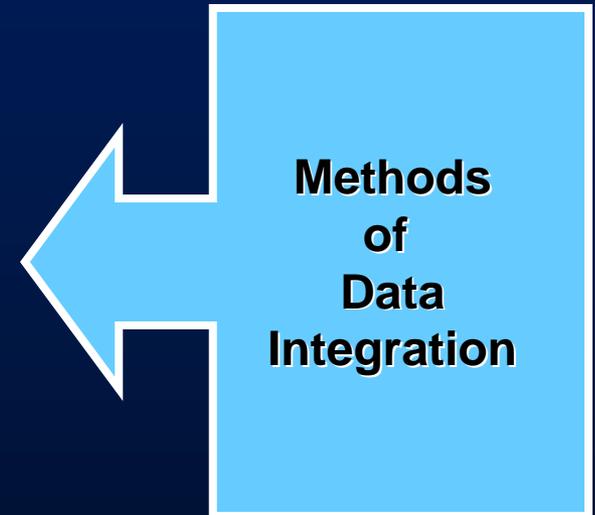
Use Simultaneous:

Meta-analysis

Network meta-analysis

Cross-design synthesis

Bayes factors



# Rethinking Analytical Strategies for Surveillance of Medical Devices

## *The Case of Hip Arthroplasty*

*Sharon-Lise Normand, PhD,\* Danica Marinac-Dabic, MD, PhD,† Art Sedrakyan, MD, PhD,†  
and Ronald Kaczmarek, MD, MPH†*

**Background:** Randomized trials that sometimes serve as the basis for device approval are small, short term, and generalizable to an increasingly smaller percentage of patients. Some of the most common and challenging devices are those used in hip replacement. Artificial hips are implanted in thousands to alleviate pain caused by noninflammatory joint disease and to restore patient mobility. During 2004 in the United States, although 68% of hospital stays for partial or total hip replacements were for those aged 65 years and older, younger patients will account for 52% by 2030.

**Methods:** Using hierarchical modeling, we propose a framework for combining information from premarket and postmarket settings. Our key assumption is that device performance characteristics and outcomes obtained from 1 cohort are related to device characteristics and outcomes of the same or similar devices observed in other cohorts. We illustrate methods by jointly modeling Harris Hip Scores (HHSs) and revision-success data from 1851 subjects who participated in 3 pivotal randomized or observational studies of artificial hips.

**Results and Conclusions:** Subjects participating in randomized studies had better 2-year HHS than those in observational studies (posterior mean increase in HHS = 4.1, posterior standard deviation = 0.6). Patients implanted with ceramic-on-polyethylene hip used in 1 study had higher 2-year HHS than those implanted with a different ceramic-on-polyethylene hip in another study (mean difference = 4.2, standard deviation = 0.6). Our approach is feasible and will advance regulatory science using a transparent and dynamic new paradigm for knowledge management throughout the total product life cycle.

**Key Words:** crossdesign synthesis, network meta-analysis, Bayesian hierarchical models, posterior distributions

*(Med Care 2010;48: S58–S67)*

Current approaches for integrating clinical information in clinical trials and real-world settings of medical devices require updating. This need arises due to the recognition of at least 2 facts. First, randomized controlled trials (RCTs), when serving as the basis for new device approval, are small, short term,<sup>1</sup> and are generalizable to an increasingly smaller percentage of patients. The reasons for decreased generalizability is 2-fold: (1) the population is aging, having more chronic diseases, and comprising a larger portion of routine practice yet are often excluded from trials and (2) the increasing inclusion of less sick patients who are less likely to benefit.<sup>2</sup>

Second, postmarket studies are often voluntary, have design limitations, and are difficult to execute.<sup>3</sup> Although these problems are not new, they have become increasingly important during the last decade because device technology is changing at a rapid pace, therapies are used outside their intended populations, and more representative groups of patients are likely to have differential responses to the same therapy.<sup>4</sup> A broader more inclusive group of patients means wider ranges of disease severity, of sociodemographic characteristics, of genetic characteristics, and of health-related behaviors. Consequently, the device effectiveness will be more heterogeneous.

Some of the most common and challenging devices are those used in hip replacement. A total hip replacement involves cutting off the top of the femur, inserting a stem (with a femoral ball) into the femur, and replacing the hip's socket, which will articulate with the femoral ball. Patient enrollment and retention in the pre or postapproval study setting pose unique problems in assessing hip replacement systems because long-term follow-up, generally 10 years postimplantation, is required. Blinding and allocation concealment in RCTs are difficult, and the numerous potential comparators requires very large numbers of patients to be studied. Device



# Focus on Strategic Partnership





# FDA Medical Device Epidemiology Network Initiative



## “MDEpiNet”

### MISSION

To bridge evidentiary gaps, to develop infrastructure and innovative methodological approaches for conducting robust studies to improve medical device safety and effectiveness understanding throughout the device life cycle.

### OBJECTIVES

Improve the paradigm of how medical device knowledge is utilized throughout device life cycle

Leverage partner resources and expertise to create a sustainable, robust infrastructure through which stakeholders will continue to gain valuable knowledge about medical devices

Become fully integrated in the systematic evaluation of medical devices and CDRH decision making

### APPROACHES

- ✓ Systematically evaluate evidence of risks and benefits associated with medical devices
- ✓ Collaborate with external parties with relevant expertise to determine evidence gaps, study questions, methodologies and best practices
- ✓ Develop and test innovative methodological approaches for medical device research and regulatory science
- ✓ Disseminate the findings to all stakeholders

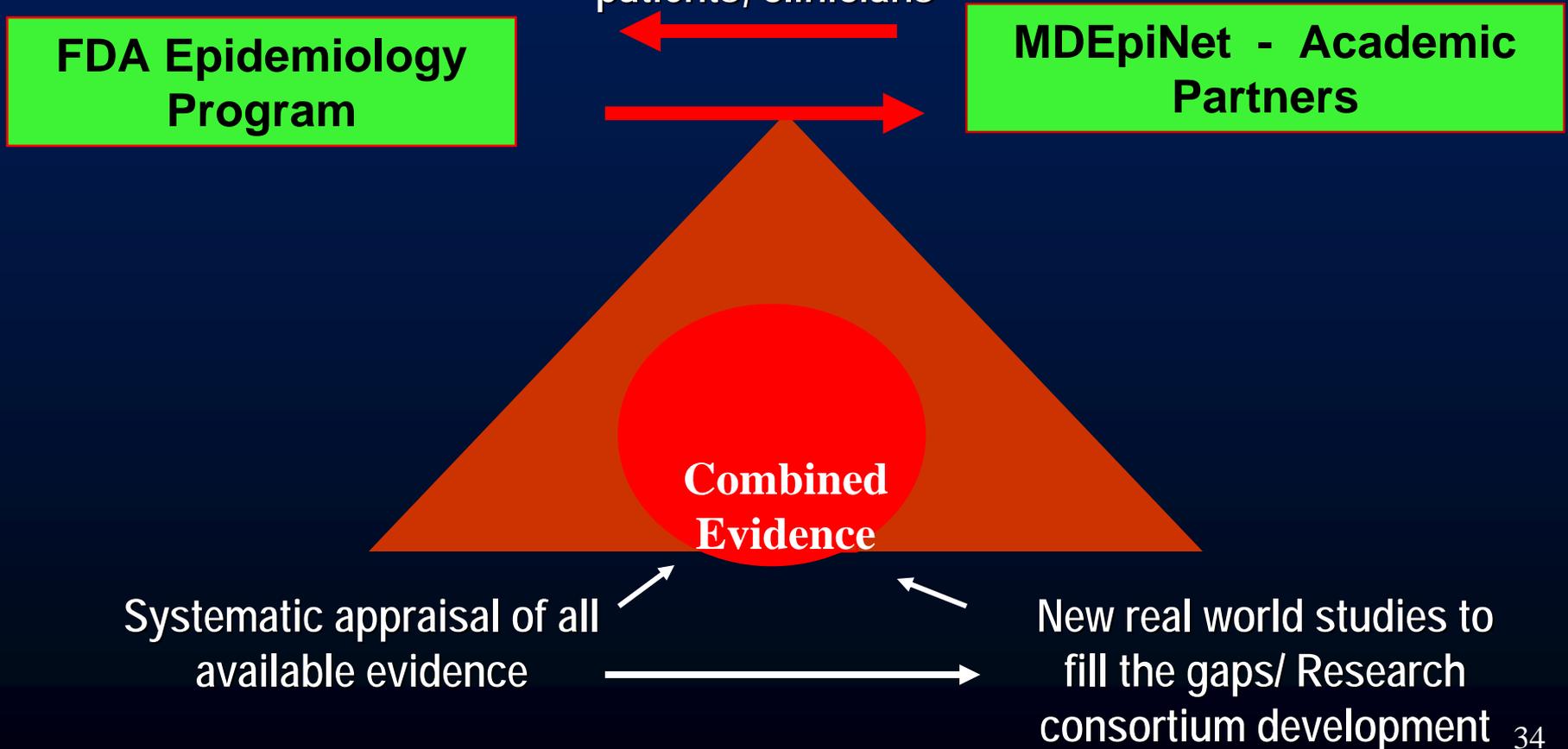


# MDEpiNet



# MDEpiNet conceptual framework

Translate the results for regulatory decision making and dissemination for patients, clinicians



# MDEpiNet – Unique Role

- Will provide tools such as:
  - Study design for distributed network based research collaboration
  - Advanced analytical overall methods such as multilevel analyses (hospital, surgeon, patient)
  - Advanced analytical methods for confounding adjustment - propensity scores, instrumental variables
  - Cross design syntheses and Bayesian methods
  - Help strengthen relationships and stakeholder development

# Upcoming Epidemiology Outreach Efforts

- ✓ IDEAL/TPLC Conference Dec/2011
- ✓ 522 Studies Conference Mar/2012
- ✓ MDEpiNet Conference Apr/2012
- ✓ PAS Studies Conference May/2012
- ✓ Registries Conference Jun/2012

# Thank you!

[danica.marinac-dabic@fda.hhs.gov](mailto:danica.marinac-dabic@fda.hhs.gov)

(301) 796-6689

