



BRIGHAM AND
WOMEN'S HOSPITAL

Current Issues in Device Development and Approval – An Academic Perspective

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Disclaimer

The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.

Academic Criticism of Medical Device Approval

- clinical trials not always performed for new product approval
- clinical trials frequently not randomized
- clinical trials are small
- clinical trials are exclusive (sites, patients)

“Opening the FDA Black Box”

Goodman and Redberg. *JAMA*. 2014;311(4):361-363.

Drug pivotal trial design is variable across indications:

- one RCT instead of 2

- lack of active comparator

- non-inferiority design

- surrogate endpoints

- non randomized trials

- short trial durations (e.g. <6m)

Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. *JAMA*. 2014;311(4):368-377.

“Opening the FDA Black Box”

Goodman and Redberg. *JAMA*. 2014;311(4):361-363.

Premarket approval (PMA) commonly includes single arm studies

510K pathway and PMA supplements for medical devices often approved without clinical testing

Dhruva SS, Bero LA, Redberg RF. Strength of study evidence examined by the FDA in premarket approval of cardiovascular devices. *JAMA*. 2009;302(24):2679-2685.

Institute of Medicine. *Medical Devices and the Public's Health: The FDA 510(K) Clearance Process at 35 Years*. Washington, DC: National Academies Press; 2001.

Rome BN, Kramer DB, Kesselheim AS. FDA approval of cardiac implantable electronic devices via original and supplement premarket approval pathways, 1979-2012. *JAMA*. 2014;311(4):385-391

Limited breadth of trial populations

Trials for approval focus on narrow clinical inclusion criteria

Even with broader criteria, <50% eligible subjects provide consent

Unrepresented patients have higher rates of adverse outcomes

Win HK et al. JAMA. 2007 May 9;297(18):2001-9.

Beohar N et al. JAMA. 2007 May 9;297(18):1992-2000.

de Boer SP et al. Eur Heart J. 2011 Sep;32(17):2161-7.

What is unique about devices?

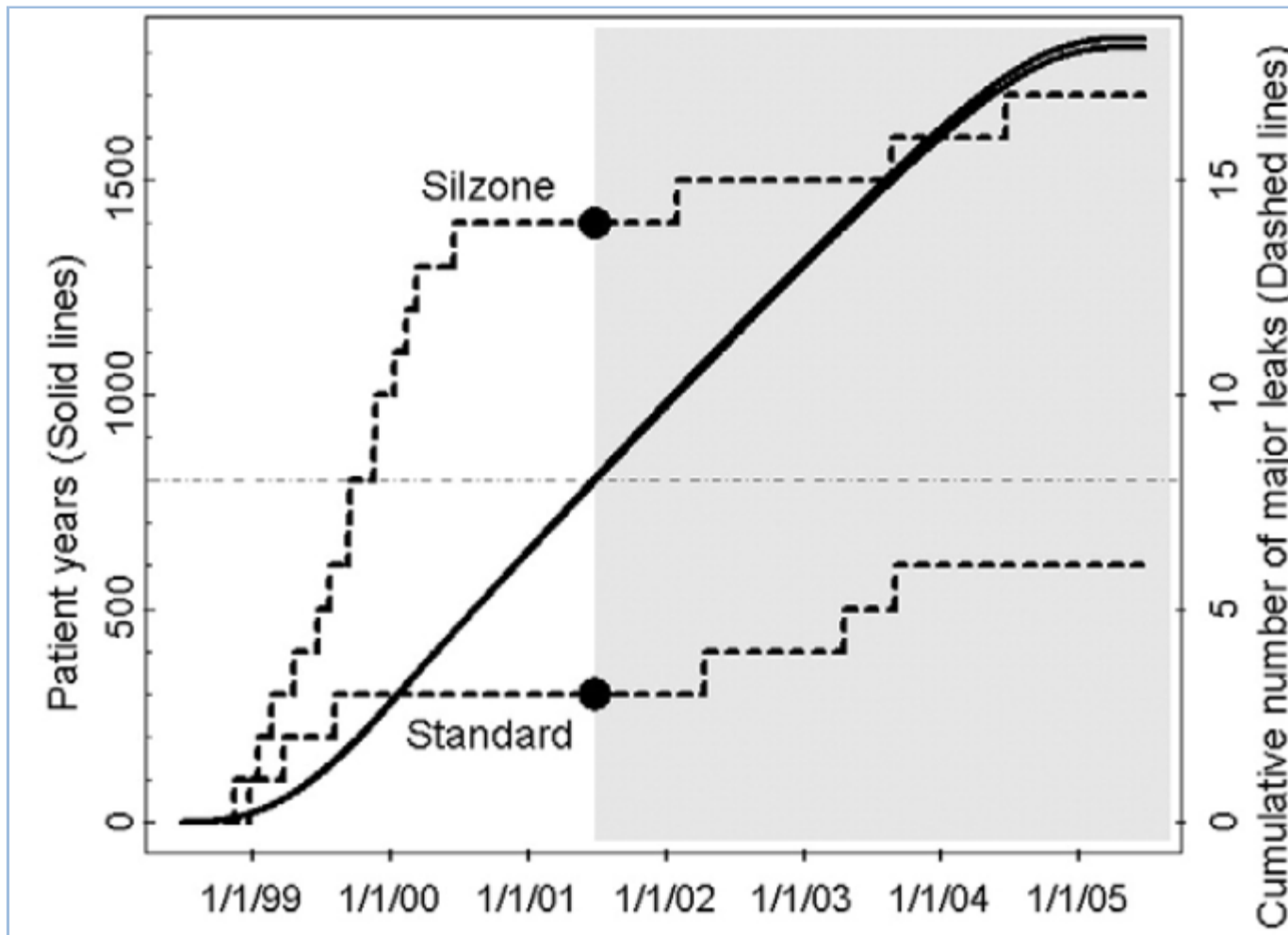
Iterative improvement based on mechanical design

Failure mode may be predicted by either bench testing or detected in early single arm safety studies

Short product life cycle

Range of appropriate trial designs

- Bare metal stent primary failure mode is known – incomplete expansion
- Small procedural single arm studies are sufficient for approval



Prosthetic Heart Valves: Objective Performance Criteria Versus Randomized Clinical Trial

Gary L. Grunkemeier, PhD, Ruyun Jin, MD, and Albert Starr, MD (Ann Thorac Surg 2006;82:776–80)

Prior Experience Developing an OPC for BMS

STATISTICS IN MEDICINE

Statist. Med. 2003; **22**:313–336 (DOI: 10.1002/sim.1337)

Application of models for multivariate mixed outcomes to medical device trials: coronary artery stenting

A. James O'Malley^{1,*,\dagger}, Sharon-lise T. Normand^{1,2} and Richard E. Kuntz³

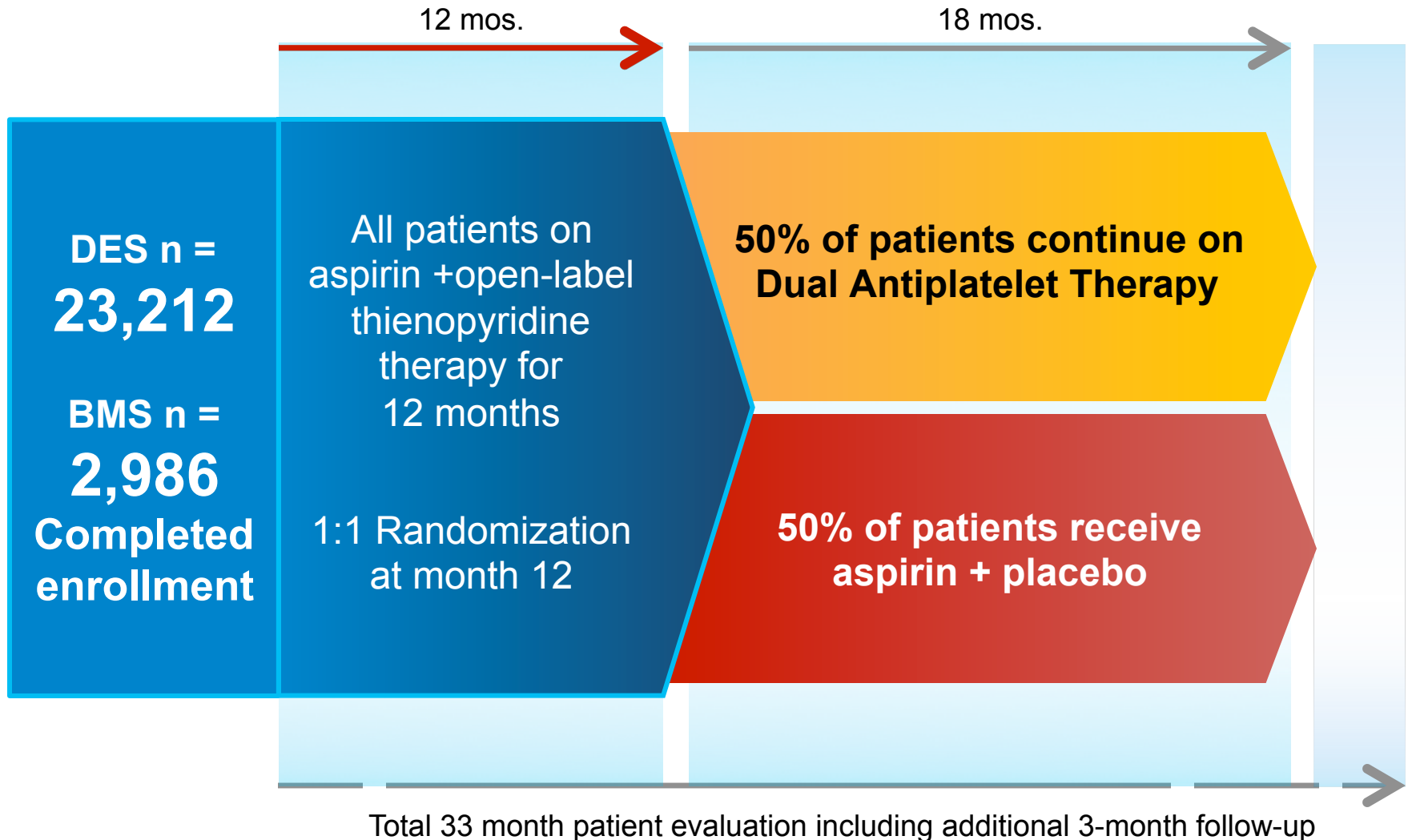
- >5000 patients with 1 year follow up in RCT
- Multivariate OPC with modelling of impact of known risk factors for restenosis as empirically observed

Dual Antiplatelet Therapy Study

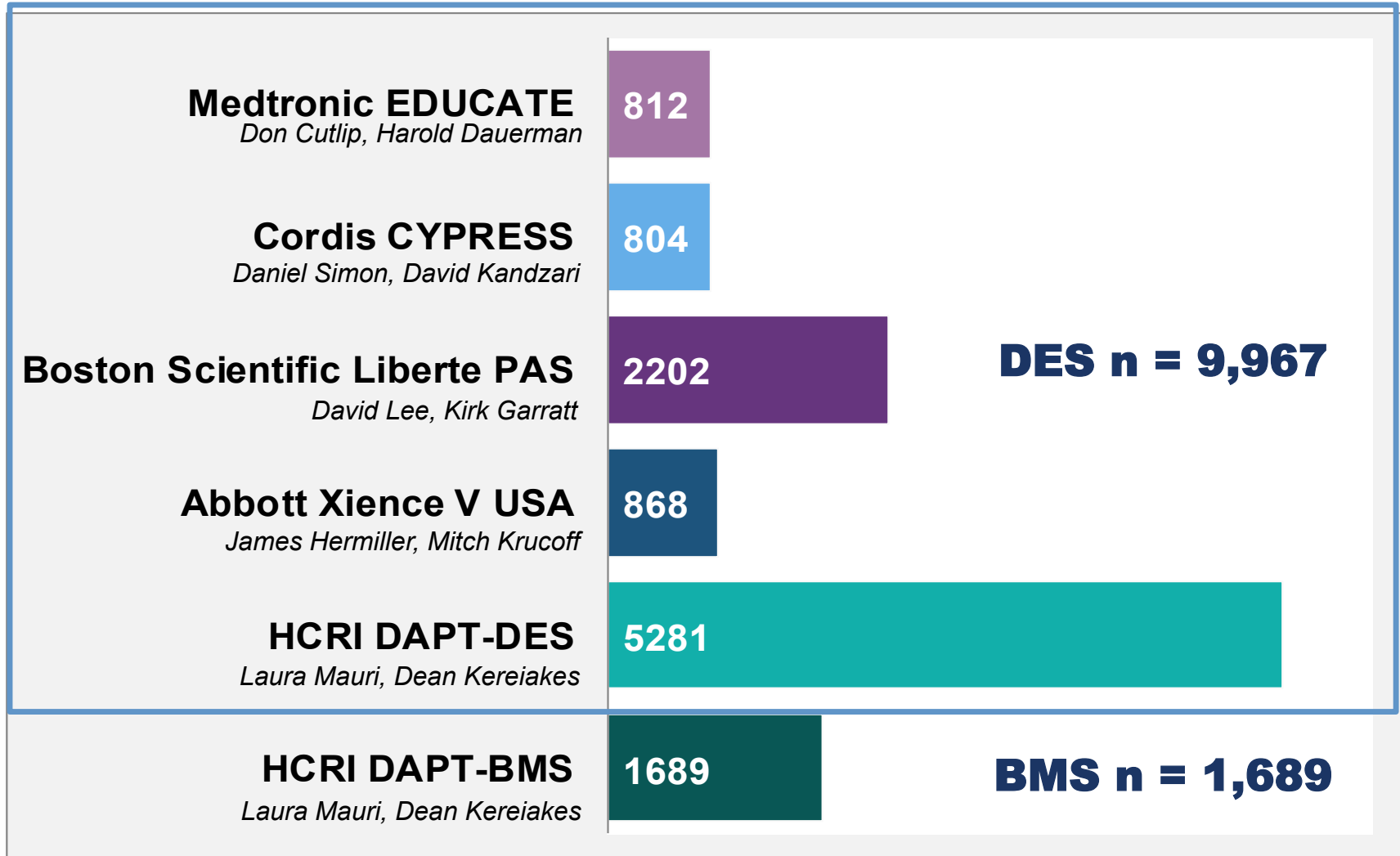
March 2008 Statement of FDA Principles:

- A need for a large, pragmatic public health trial exploring the benefit of extending thienopyridine treatment beyond one year in patients treated with DES needs to be done expeditiously
- FDA expects that the results of the study will change clinical practice and provide valuable new information in product labeling for DES.

Design



Randomization completed 2012



Primary Endpoint Results Expected 2014

Dual Antiplatelet Therapy Study

- FDA – streamlining and active engagement in study execution
- Academia – simplified data collection, limited secondary data collection, but adjudication of key endpoint data
- Industry – cooperative interaction, willingness to support a study to advance clinical practice without competitive value
- Patients and physicians -- enthusiastic participation and enrollment

Quality in medical device evaluation

Each study with a specific objective

Designed to address key areas of uncertainty

Tested in a population with unmet need

Comparison of efficacy and safety to current standards of care

Feasible to conduct

Reliable to make inference from to clinical practice

Examples

1. Objective performance criteria for surgical heart valves
2. Blinded randomized trial with surrogate endpoint for renal denervation
3. Open label randomized trial compared with medical therapy with mortality endpoint for percutaneous heart valves

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How we achieve Quality in Clinical Research

- Well-defined objective
- Reliable results
- Feasible conduct
- Clinical impact

The Real Priorities for High Quality Trials for Medical Device Approval

1. Application of methods to maximize efficiency and minimize bias – RCT, single arm studies, surrogate endpoints, missing data
2. Expediting enrollment and follow-up completeness – Large simple trials, risk based monitoring, registry based clinical trials
3. Improving trials infrastructure – contracting, reimbursement, IRB, site selection, patient/subject engagement

Ensuring quality in clinical research

- Fulfills regulatory, business and scientific needs, but also *ethical* obligations to subjects
- Subjects volunteer time and consent to unknown risks
- These contributions are altruistic
- Trial designs that improve efficiency, minimize bias, and ensure reliable data ascertainment help fulfill an obligation to human subjects to value these contributions

Device Development and Approval – An Academic Perspective - Conclusions

- Clinical trials and programs should be tailored to address uncertainty regarding safety and effectiveness
- While RCT are the best method to eliminate bias, no one size design fits all
- Key challenges extend from design through to execution
- Ensuring quality is key to bringing medical progress to patients