Tailoring best practices for the evaluation of endpoints in clinical device trials

George Dangas, MD, PhD

Cardiac Safety Research Consortium

11th March, 2016

ROADMAP

- Study blinding challenges
- Variability in Operator Expertise and Learning Curves
- Gathering necessary data for adjudication
- Role of Core Labs
- Standardized Endpoint Definitions

Study blinding challenges

- Who has access rights to study information?
- Different site personnel to perform the procedure vs. the follow-up so the treatment will remain blinded during the follow-up
- What information can be provided and by what method?

Hicks et al JACC 2014

Study blinding challenges

- Limit access to data
- Shred printed items unless required for recordkeeping. Do not place in trash
- Provide private areas for data review, analysis, and data entry.
- Ensure that all relevant clinical information that may infer or confirm treatment arm is appropriately redacted from source documents.

Issues with study blinding

- GPs are nervous when dealing with blinded drug regimens
- It might affect the entire patient's medical treatment
- Accuracy issues with procedure reports
  - Impact on patient care (stent vs stent or sham vs active intervention)

What to do if unblinding is necessary?

- When it should occur
- How does it occur
- Who will have access to the unblinded informatio

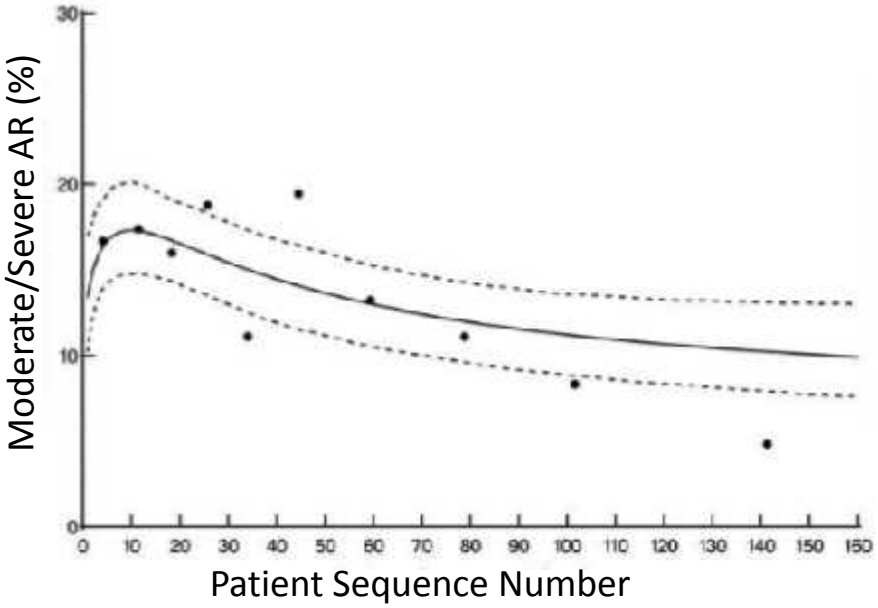
Variability in Operator Expertise and Learning Curves

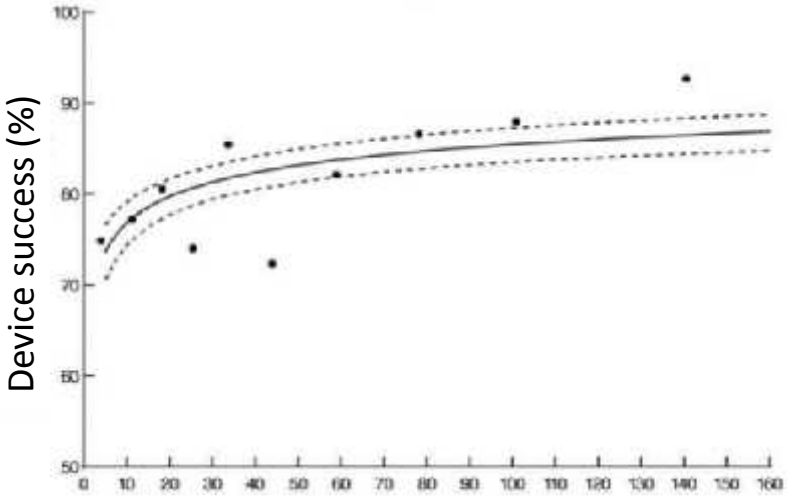
- In case of unexperienced operators more adverse events could be observed because of the operator skills instead of the study device
- During a longer run in period, the number of events that happen early in the trial because of operator inexperience could be better identified as compared to the event rate in the rest of the trial
- Adequate roll-in cases (vs impact of too many roll-in cases in case selection)

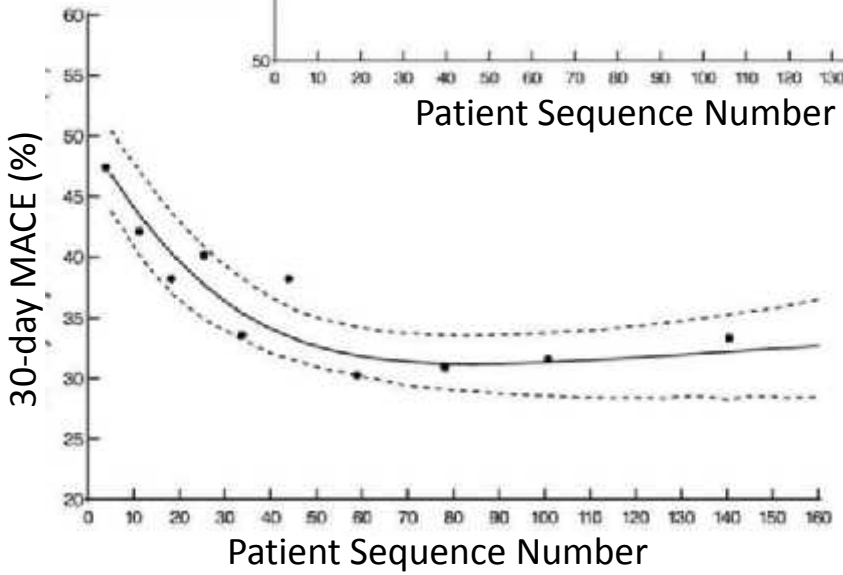
Variability in Operator Expertise and Learning Curves

Learning Curves for Transfemoral Transcatheter Aortic Valve Replacement in the PARTNER-I Trial: Success and Safety

Sa'ar Minha,[1] MD, Ron Waksman,[1*] MD, Lowell P. Satler,[1] MD, Rebecca Torguson,[1] MPH, Oluseun Alli,[2] MD, Charanjit S. Rihal,[3] MD, Michael Mack,[4] MD, Lars G. Svensson,[5,6] MD, PhD, Jeevanantham Rajeswaran,[5,6] PhD, Eugene H. Blackstone,[5,6] MD, E. Murat Tuzcu,[6] MD, Vinod H. Thourani,[7] MD, Raj Makkar,[8] MD, John Ehrlinger,[6] PhD, Ashley M. Lowry,[6] MS, Rakesh M. Suri,[6] MD, DPhil, Kevin L. Greason,[3] MD, Martin B. Leon,[5,9] MD, David R. Holmes,[3] MD, and Augusto D. Pichard,[1] MD



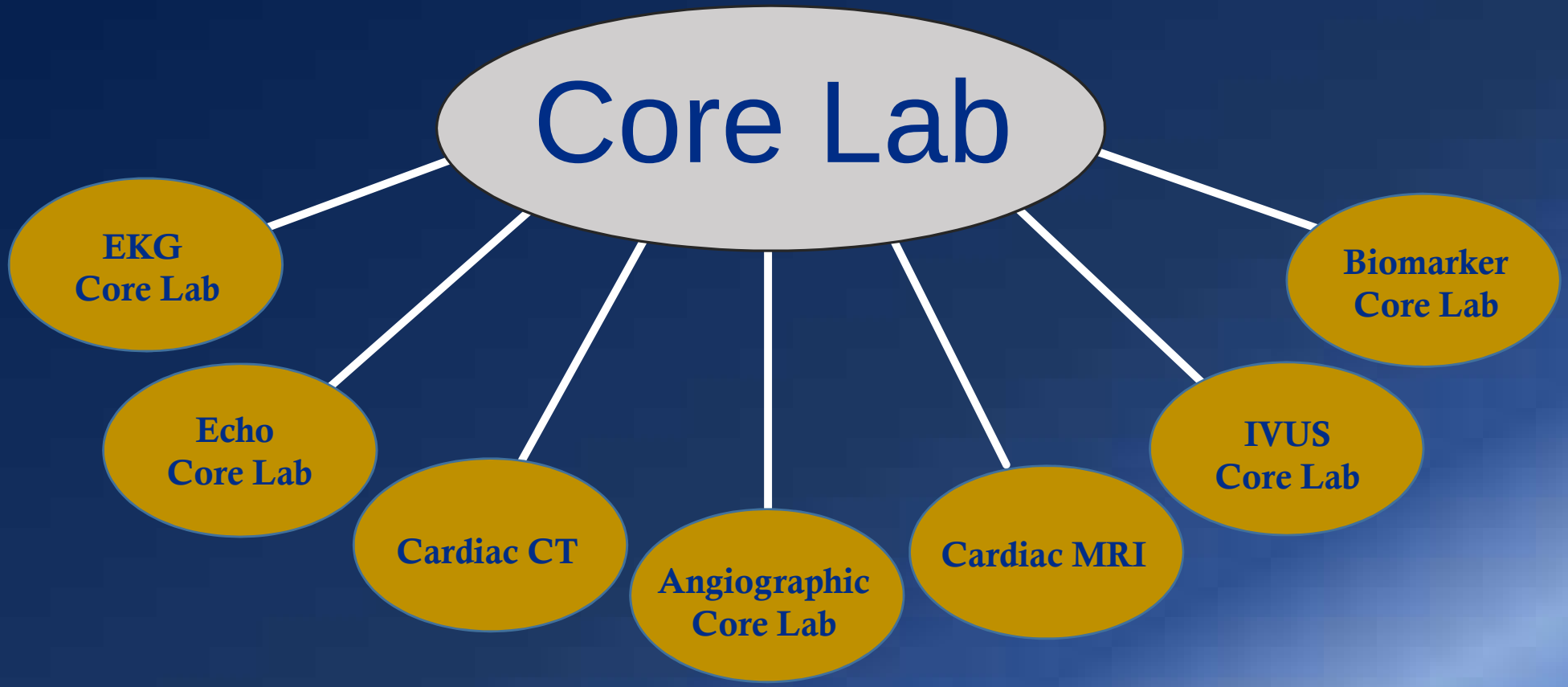




Gathering necessary data for adjudication

- Comprehensive reports of patient history and adverse events
- Redacted Source documents deemed relevant as pre-specified in the study protocol: discharge summary, clinical diary, lab test, etc.
- If insufficient source documents are available, the Clinical Events Committee (CEC) should make every effort to obtain all the necessary documents before final adjudication
- It should be clear if/when no further documentation will be available before reporting the case to the CEC

Cardiovascular Core Labs



Role of Core Labs

- Provide central reading/analysis for images generated at enrolling centers
- Reduce variability in interpretations with the use of a limited number of experienced observers with standardized training
- Generate a high quality database that can be integrated with the clinical data
- Monitor image quality
- Impact of delayed image analysis (feedback to sites, PIs, oversight bodies)

Organization of Core Labs

- Training – Develop image acquisition protocol
- Image analysis
    - Completion of case report form
    - No clinical information that might affect image interpretation
- Data management
    - Tracking images and forms
    - Data checking and data transfer
- Audit

Organization of Core Labs

- Clinical Study protocol
- Study specific Standard Operating Procedures (i.e. Echo Core lab SOP)
- Equipment logs, inventory and maintenance
- Personal records (training logs and certifications)
- Institutional Policies and Procedures

SCIENTIFIC COMMUNITY EFFORT

Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials

Karen A. Hicks, H. M. James Hung, Kenneth W. Mahaffey, Roxana Mehran, Steven E. Nissen, Norman L. Stockbridge, Shari L. Targum, Robert Temple;
on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative

Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document*

A. Pieter Kappetein, Stuart J. Head, Philippe Généreux, Nicolo Piazza, Nicolas M. van Mieghem, Eugene H. Blackstone, Thomas G. Brott, David J. Cohen, Donald E. Cutlip, Gerrit-Anne van Es, Rebecca T. Hahn, Ajay J. Kirtane, Mitchell W. Krucoff, Susheel Kodali, Michael J. Mack, Roxana Mehran, Josep Rodés-Cabau, Pascal Vranckx, John G. Webb, Stephan Windecker, Patrick W. Serruys, and Martin B. Leon

Standardized Bleeding Definitions for Cardiovascular Clinical Trials

A Consensus Report From the Bleeding Academic Research Consortium

Roxana Mehran, MD; Sunil V. Rao, MD; Deepak L. Bhatt, MD, MPH; C. Michael Gibson, MS, MD; Adriano Caixeta, MD, PhD; John Eikelboom, MD, MBBS; Sanjay Kaul, MD; Stephen D. Wiviott, MD; Venu Menon, MD; Eugenia Nikolsky, MD, PhD; Victor Serebruany, MD, PhD; Marco Valgimigli, MD, PhD; Pascal Vranckx, MD; David Taggart, MD, PhD; Joseph F. Sabik, MD; Donald E. Cutlip, MD; Mitchell W. Krucoff, MD; E. Magnus Ohman, MD; Philippe Gabriel Steg, MD; Harvey White, MB, ChB, DSc

Standardized Endpoint Definitions

- Standardized endpoint definition must be clearly stated in the protocol
- Facilitate the consistent, accurate, and reproducible capture of clinical concepts; standardize the terminology used to describe cardiovascular diseases and procedures; create a data environment conducive to the assessment of patient management and outcomes for quality and performance improvement and clinical and translational research
- Pivotal for correct event adjudication by the CEC
- Necessary for comparing results across multiple studies

Weintraub et al 2015 JACC

3 Main Biases of Renal Denervation Trials

- **Regression to the mean**: This is caused by the tendency to select patients for studies for new HTN therapies when their blood pressures (BP) at enrollment are higher than their individual long-term averages. A control group protects against this type of bias
- **Asymmetrical data handling**: results from the physicians re-measuring BP after an intervention believed to be effective if the initial reading does not show a change. Either blinding physicians to treatment allocation or removing them from data collection protects against this source of bias
- **Confounding or nondenervation effect**: This occurs when true BP drops are caused by something other than the procedure, such as an increase in drug adherence or placebo effect.

Sham/Mock Interventions

- Remove bias related to the procedure
- Help to discern between procedure/operator related events and device related events
- Must receive ethical committee approval

Trained to perform invasive interventions only for the medical benefit of patients, they find themselves administering fake procedures. Moreover, they must manipulate the performance so as to create a false belief in patient-subjects that a real procedure is being administered—a deception that may have to be maintained in follow-up visits

Miller G 2004 JRSM

Sham/Mock Interventions

ARGUMENTS IN FAVOR

Increase the scientific validity and the benefits to society while at the same time the risks and harm can be acceptable.

ARGUMENTS AGAINST

- they pose unacceptable risks to participants, and present difficulties with informed consent
- the use of deceptive tactics is unethical, and that the feasibility of such controls is compromised because of a lack of public support.

Niemansburg SL 2015 Surgery

LESSON LEARNED

SYMPLICITY HTN-2

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

Symplicity HTN-2 Investigators[‡]

Conclusions

Catheter-based renal denervation can safely be used to substantially reduce blood pressure in treatment-resistant hypertensive patients.

Over 50% of SYMPLICITY HTN-**3** cases were from sites with under 2 total procedures. With 6 procedures a site was at top 10% in SYMPLICITY HTN-**3** site rank!

SYMPLICITY HTN-3

A Controlled Trial of Renal Denervation for Resistant Hypertension

Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D., William W. O'Neill, M.D., Ralph D'Agostino, Ph.D., John M. Flack, M.D., M.P.H., Barry T. Katzen, M.D., Martin B. Leon, M.D., Minglei Liu, Ph.D., Laura Mauri, M.D., Manuela Negoita, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Oparil, M.D., Krishna Rocha-Singh, M.D., Raymond R. Townsend, M.D., and George L. Bakris, M.D., for the SYMPLICITY HTN-3 Investigators*

Conclusions

This blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control