Real World Evidence: Expectation From Industry

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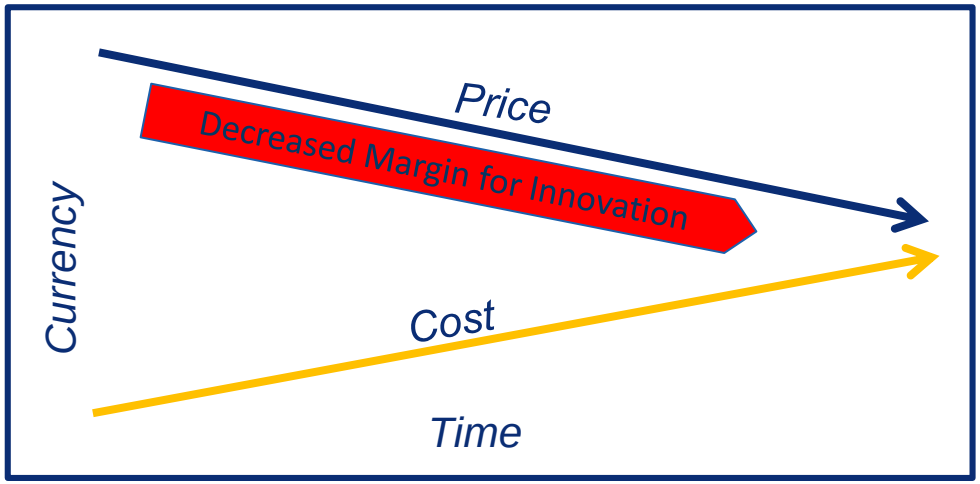
Disclosure Statement of Financial Interest

I, Neal Fearnot, am an employee of Cook Medical. My employment with Cook does not present a conflict of interest in the context of the subject of this presentation.

2017…

Industry's Reality: Mounting Costs and Lower Prices Leads to a Reassessment of Investment



COST DRIVERS:
Global pre-market regulatory requirements
Global compliance requirements
Development costs
Global reporting burden
Tax burden
Support for multiple initiatives, societies, etc.
Supply chain, Infrastructure

We have shown this chart for years. Cost is an ever-present concern for industry and limits our ability to serve patients and all stakeholders.

Will RWE reduce clinical data costs?

History of Industry's Needs in the HBD Setting
Real World Evidence is a Current Focus

Year	Industry's needs in the HBD setting
2004	Understanding Device Lag in Coronary Stents, 2.5 years from EU to US and 2.5 years from US to JP Timely access to patients/physicians in Japan (integrated definitions; site visits)
2005-07	Infrastructure improvements to support clinical research
2008	Trial design improvements toward US/Japan Single Protocol Poolable trial data (concomitant enrollment; common outcomes)
2009	Collaborative Scheme POCs/Concurrent trials and regulatory process (Proof of Concept projects - first two clinical trial POCs selected; linking post-market surveillance with INTERMACS)
2010-11	Transportability of data (harmonized GCP, STED, inspection process)
2012-13	Regulatory synergies (testing to globally accepted standards; global clinical trials)
2014	Understanding burden of innovation in a global environment with decreasing price and increasing cost
2015	Global clinical programs incorporating both global and regional studies, with common definitions and endpoints to meet the needs of multiple stakeholders
2016	Post-market data faster, cheaper and of more value
2017	Real World Evidence, Pediatrics, Early Feasibility

RWE is one of HBD's Current interests.

Agenda

In the context of RWE, what does industry need in order to mitigate risk and gain benefit for the patient and all stakeholders?

- Assurance of privacy of company confidential information and patient information
- Protection from unintended consequences of exploring novel regulatory pathways
- Functional global research infrastructure
- Precompetitive collaboration, trust and good will
- Predictability in development, regulatory and reimbursement
- Efficient pre-market clinical data collection
- Meaningful, cost-efficient post-market data collection

Privacy of Company/Patient Confidential Information

- Company data and strategies
  - Assurance needed as company confidential information is released to registries and other instruments for collection of real world evidence
- Challenge to patient privacy
  - Appropriate patient consenting for registries and electronic health records
  - Challenge to effectively access, extract and aggregate data from existing electronic health data sources and load into a secondary source (registry)
  - Maintaining patient privacy while building longitudinal records

Protection From Unintended Consequences

- Novel regulatory pathways may bring unintended consequences
- Companies need reassurance that good faith efforts and willingness to try novel pathways will be appropriately supported
- HBD creates an atmosphere of trust through transparency of non-confidential information, limiting the risk of novel pathways
- Several HBD POCs participated in the pilot program for sharing information between US FDA and Japan MHLW/PMDA.
- Industry concerns that the process would slow review were unfounded as regulators from both sides supported the collaborative process.

Functional Research Structure

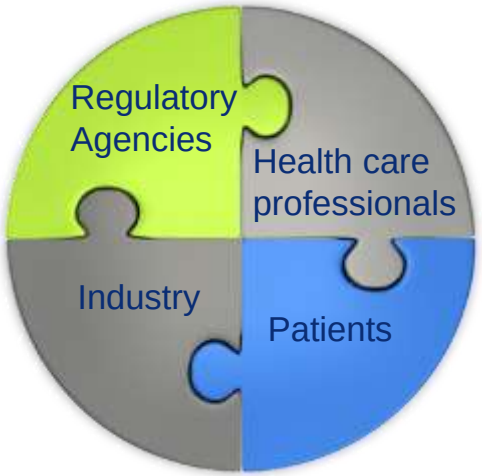
Industry investment in clinical studies demands a functional research infrastructure.

- Organize/structure the company to prepare global submissions simultaneously
- Provide adequate in-house resources to staff parallel programs
- Assign top engineers and technical staff with good communication skills to simultaneous US/Japan submissions
- Enable close communication between US and Japan project teams (regular calls and meetings, webex availability, shared milestones)
- Be sure US side understands information needed to meet Japan's approval criteria (e.g., engineers write test reports to include all data needed in both countries)
- Include information needed for Japan in raw material database
- Use templates cross-referencing similar data in Shonin(STED) vs PMA
- Minimize translation delays; enable high quality translation
- Provide for version control, regulatory professional proof reading, back translation of modifications to translated documents
- Use Global SOPs

Precompetitive Collaboration, Trust and Good Will

Strength of HBD – Relationships

- Appropriate, pre-competitive support among regulators, industry and academia…
- Working together
- Building communication and trust
- Breaking new ground
- Establishing novel predicates
- Learning from the past
- Envisioning the future



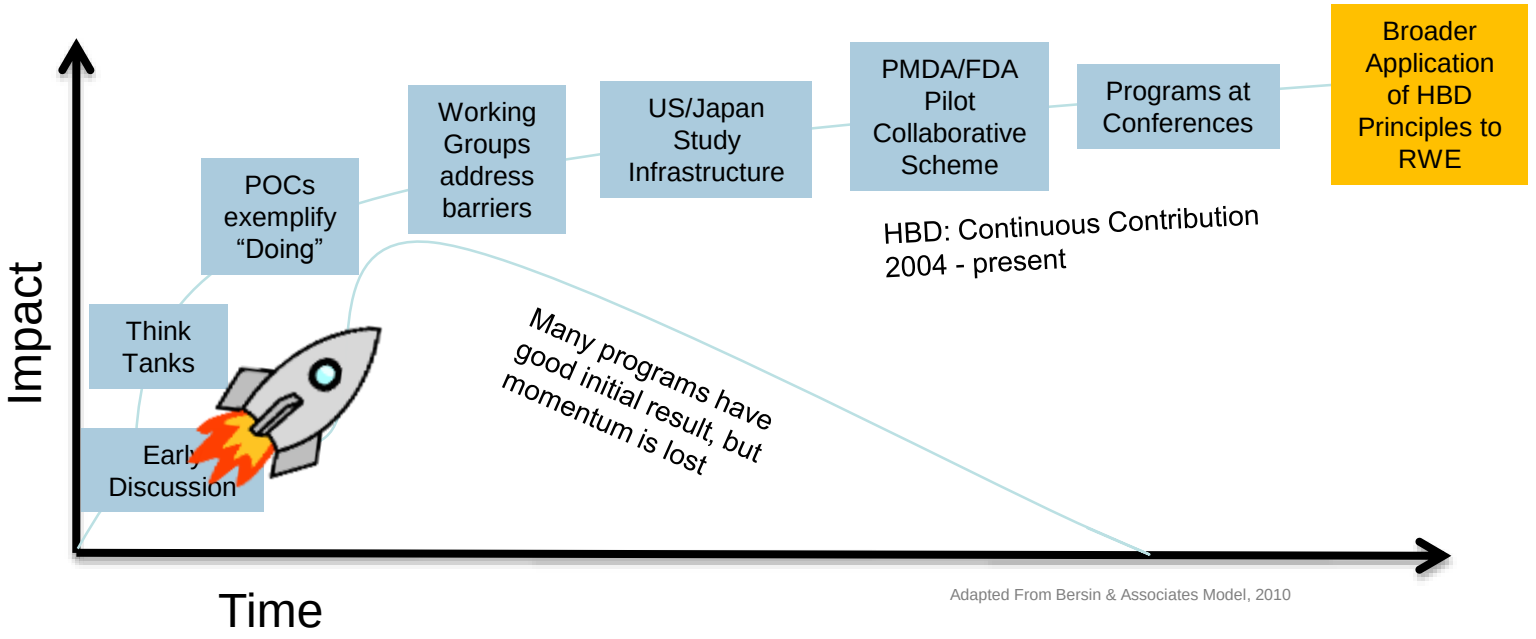
Goal of providing safe and effective products to patients by:

- better, faster, cheaper
- more predictable processes.

Predictable and Monetizable Product Development Process

- How long will it take and how much will it cost?
- Industry is willing to support the product development process only if it is accurately predictable and profitable.
- Needs help predicting and monetizing the process.

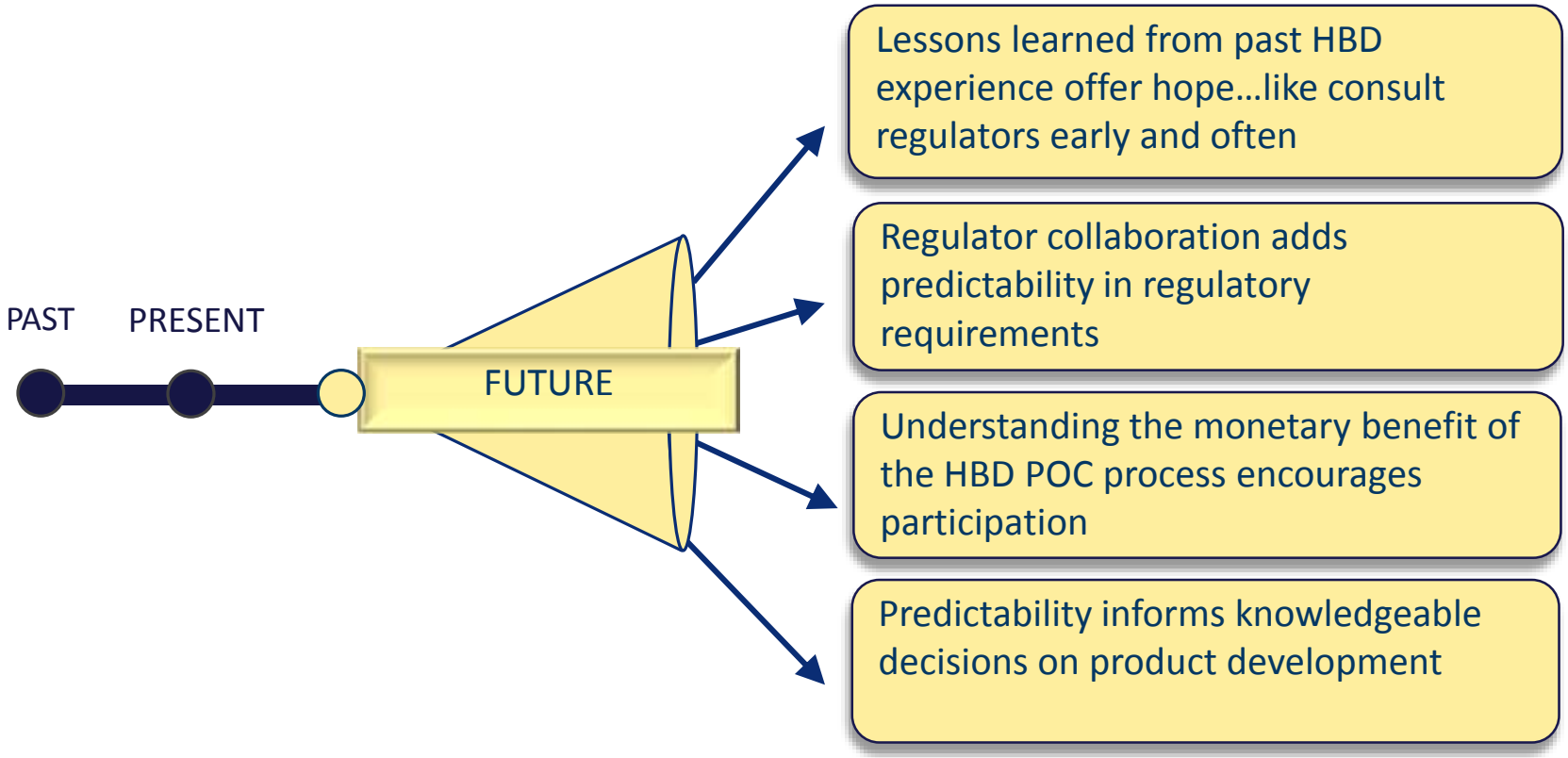
HBD: Increasing Predictability – Continuing Impact



HBD experience has increased predictability and kept momentum.

Continuing impact as global stakeholders determine ways to use RWE.

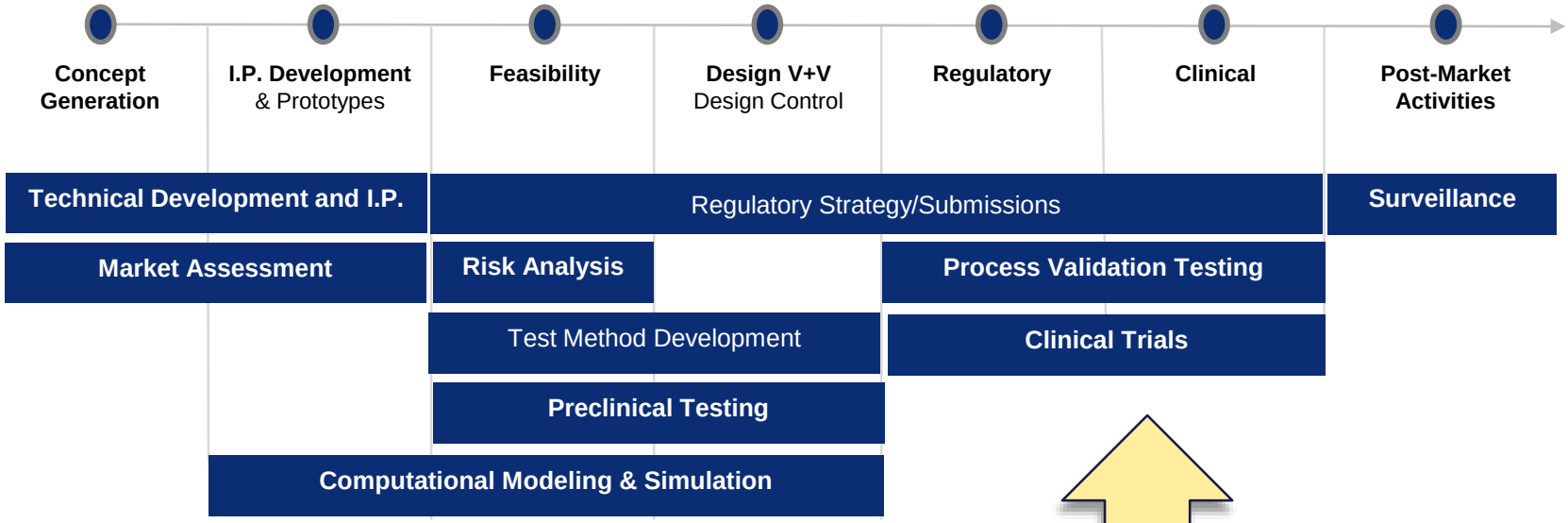
Predictability Informs Decisions



Gathering clinical evidence – how long will it take? How much will it cost?

Decision on Costly Development Sequence

Companies face lengthy, costly development sequences for breakthrough products



Would use of real world evidence reduce cost in the clinical evidence process, yielding less cost and ability to predict/monetize cost?

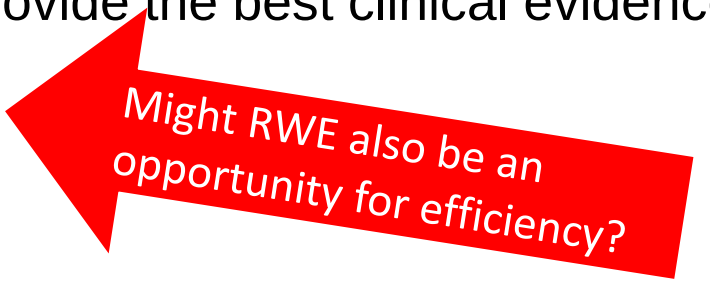
Efficiency Through Global Clinical Programs

Plan global clinical programs to most efficiently use various means of gathering clinical evidence

•Global clinical study to answer fundamental S&E (or a combination of coordinated regional studies with same definitions, endpoints and statistics). Clinical trials should include reasonable cost with targeted patient selection, reliable enrollment and achievable endpoints acceptable to regulators and meaningful to clinicians.

•Smaller studies designed for certain populations or practice patterns, or to obtain additional data on one detailed aspect of S&E.

•Real World Evidence may provide the best clinical evidence, pre-market and post-market.



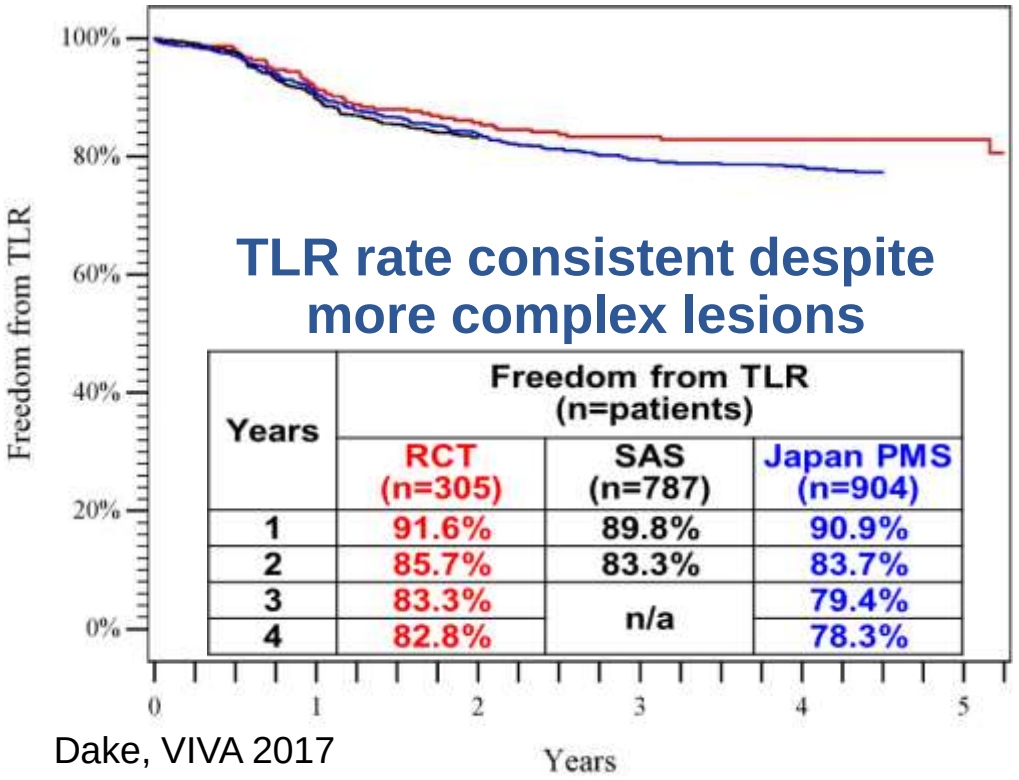
Real World Evidence – Post Market Data

Industry needs post-market data that is effective and cost-efficient:

- Data of more value (maximum useful data for money spent)
- Data faster, to detect problems quickly
- Data that balances pre- and post-market requirements
- Data to enhance patient safety (clarifications to IFU)
- Data to refine indications; identify optimal indications for optimal patient outcome

Post Market – Huge opportunity for real world evidence, if we can define regulatory process for using it appropriately.

Real World Registry May BE Useful Tools to Confirm Premarket Studies



TLR rate consistent despite more complex lesions

Years	Freedom from TLR (n=patients)		
	RCT (n=305)	SAS (n=787)	Japan PMS (n=904)
1	91.6%	89.8%	90.9%
2	85.7%	83.3%	83.7%
3	83.3%	n/a	79.4%
4	82.8%		78.3%

Dake, VIVA 2017

Freedom from TLR
(Target Lesion Revascularization)

RCT premarket results were sustained in real-world practice **(**example drug-eluting stent)

Real World Evidence Topics for HBD

- What sort of audit readiness is needed, or even feasible, when using RWE to support a regulatory decision?
- What work is needed to prepare RWE to pass a JGCP or BIMO audit? Is the amount of time and expense so great as to negate benefit?
- What is the role of foreign pivotal studies and non-confirmatory domestic trials? Can these results inform RWE?
- Can historical data from other approvals inform RWE and support regulatory submissions in the US and Japan?
- Is there possibility of an HBD POC in which RWE supports a joint regulatory submission in the US and Japan?

Opportunities To “Do”

Thank You

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