Documentation of value created by Real World Evidence (RWE): TVT Registry case study and proposed metrics

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Overview

- MDEpiNet Workgroup
- Framing the question: Does RWE provide a “better, faster, cheaper” way to generate evidence for regulatory decision making?
- Methods
- Results of the TVT case study
- Discussion
- Next Steps

MDEpiNet work group was formed to address the issues

- Includes representatives from clinical centers, registries, research scientists, and many companies including all three of the companies that make the valves for TVT.
- The TVT CRN was selected as first case study because have greatest amount of experience to date using RWE.
- Vascular Quality Initiative (VQI) was selected as second case study.
  - While fewer decisions have been made with the VQI, it is probably a more typical or model for evaluation of ROI.
- Co-Chair of work group, Jesse Berlin JnJ
- Editor of Journal of the American College of Cardiology read the draft white paper and showed interest in reviewing a final manuscript which is currently undergoing final drafting and revision.
- Thanks to John Laschinger, Changfu Wu, Doug Dumont, Erika Tang, and Tianey Ziegler.

Are CRN (coordinated registry network) studies “Better, Faster, Cheaper”?

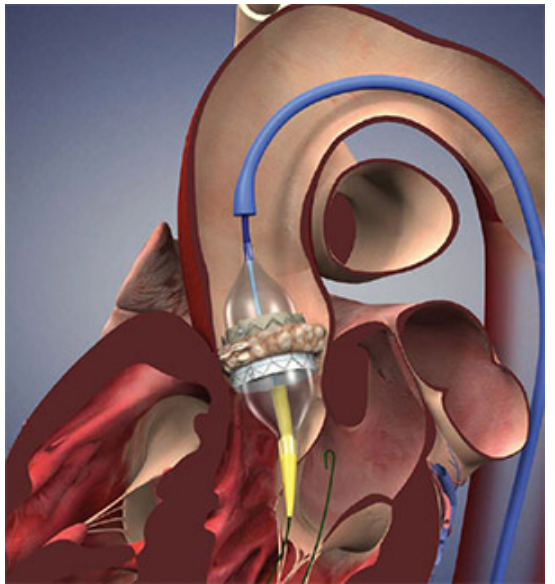
- One of the original reasons for promoting the use of RWE was to bring down the cost and time of evidence generation, and to overcome some of the limitations of the tools and methods we currently use and overcome limitations of traditional post market studies.
- Literature documenting faster enrollment using CRNs exists
  - E.g. SAFE-PCI for Women
- It makes common sense but there has not been a clear method and demonstration.

Defining terms and parameters

- CRN - Coordinated Registry Network (Doug keeps saying we should rebrand them as Coordinated RWE Networks!)
- TVT – Transcatheter Valve Therapy
- The TVT CRN case study is used because it is the most mature example of the use of RWE for device evaluation and regulatory decision making
- Return on investment (ROI) is estimated for sponsors as a group and focuses on evidence generation.
- Days saved is calculated separately for reasons explained (days saved may contribute to ROI in some circumstances)

Background

- The Transcatheter Valve Therapy Coordinated Registry Network (TVT CRN) has been used to support over 20 pre-market and post-market regulatory decisions. A method to evaluate the value created by the TVT CRN compared to traditional study designs used for device evaluation is proposed.



Methods: Data sources and linkage

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Peterson et. al

Methods: comparing CRN costs and times with “counterfactual” studies

Methods: Return on Investment (ROI) and Days Saved were calculated comparing studies that were conducted use of for the TVT CRN with “counterfactual studies,” studies that would have been done if the TVT registry did not exist. .

- Both the counterfactual cost of studies and time length of studies were projected using design specifications determined by FDA reviewers
- Cost of the studies done with the TCT CRN was provided by ACC.
- Cost of the counterfactual studies are estimated using Resnic model[1]

[1] Wimmer, Neil J. et al. “Assessing the Cost Burden of United States FDA-Mandated Post-Approval Studies for Medical Devices.” *Journal of health care finance* 2016.Spec FEATURES (2016): http://www.healthfinancejournal.com/~junland/index.php/johcf/article/view/82/83. Print.

Method: calculating costs of counterfacutal studies using the Resnic model[1]

- Briefly, the cost estimation model was developed through iterative structured interviews with 12 domain area experts in the design and management of post-approval clinical studies selected from industry, academia and clinical trial site leadership.
- Modified Delphi approach, consensus among the domain experts
- The drivers and estimates of study costs include:
  - Planned enrollment
  - Number of participating centers,
  - Duration of proposed study
  - Intensity of follow up.

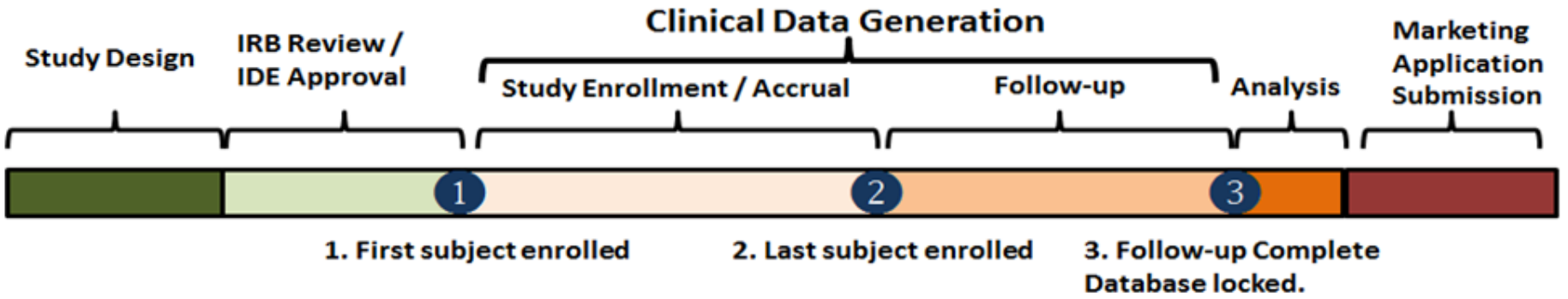
[1] Wimmer, Neil J. et al. "Assessing the Cost Burden of United States FDA-Mandated Post-Approval Studies for Medical Devices." *Journal of health care finance* 2016.Spec FEATURES (2016): http://www.healthfinancejournal.com/~junland/index.php/johcf/article/view/82/83. Print.

Resnic spread sheet

Key		1=yes, 0=no	1=yes, 0=no	1=yes, 0=no; 2=historical	#	0% - 100%	#	#	#	#	1=yes, 0=no	#	1=imaging, 2=invasive 3=other	0=cardiac, 1= non-cardiac
Scenario	Total # Subjects	Recruitment	Randomized	Control Group	Total Num Sites	Outside US %	Study Duration (yrs)	# Yrs >2 (Extension)	# Add Phone Call per Yr	# In-Person per Yr	Required Procedure?	Total Procedure Count	Type of Procedure (if yes)	Organ System
Example	1000	0	0	0	100	0%	3.0	1	0	0	1	1	2	0
P100009	2000	1	0	0	39	0%	5.0	3	0	1	1	5	1	0
P100041	1100	1	0	0	27	0%	5.0	3	0	1	1	5	1	0
P100041/S039	100	1	0	0	27	0%	5.0	3	0	1	1	5	1	0
P110021	1700	1	0	0	27	0%	5.0	3	0	1	1	5	1	0
P110021/S026	100	1	0	0	27	0%	5.0	3	0	1	1	5	1	0
P130009	1000	1	0	0	28	0%	5.0	3	0	1	1	5	1	0
P130009/S034	200	1	0	0	28	0%	5.0	3	0	1	1	5	1	0
P130009/S057	1000	1	0	0	57	0%	10.0	8	0	1	1	7	1	0
P140031	1000	1	0	0	29	0%	5.0	3	0	1	1	5	1	0
P140031/S010	1000	1	0	0	57	0%	10.0	8	0	1	1	7	1	0
P130021	1000	1	0	0	41	0%	5.0	3	0	1	1	5	1	0
P130021/S002	1000	1	0	0	45	0%	5.0	3	0	1	1	5	1	0
P130021/S010	200	1	0	0	37	0%	5.0	3	0	1	1	5	1	0
P130021/S014	250	1	0	0	24	0%	5.0	3	0	1	1	5	1	0
P130021/S016	250	1	0	0	24	0%	5.0	3	0	1	1	5	1	0
P130021/S025	100	1	0	0	41	0%	5.0	3	0	1	1	5	1	0
P130021/S033	1000	1	0	0	65	0%	10.0	8	0	1	1	7	1	0

Methods: Time-savings analysis (Days-saved)

Time frame from study design to Marketing Application Submission.



CET = (number of patients for study by design / rate of enrollment) / study duration specified by design

Methods: Cost-savings analysis

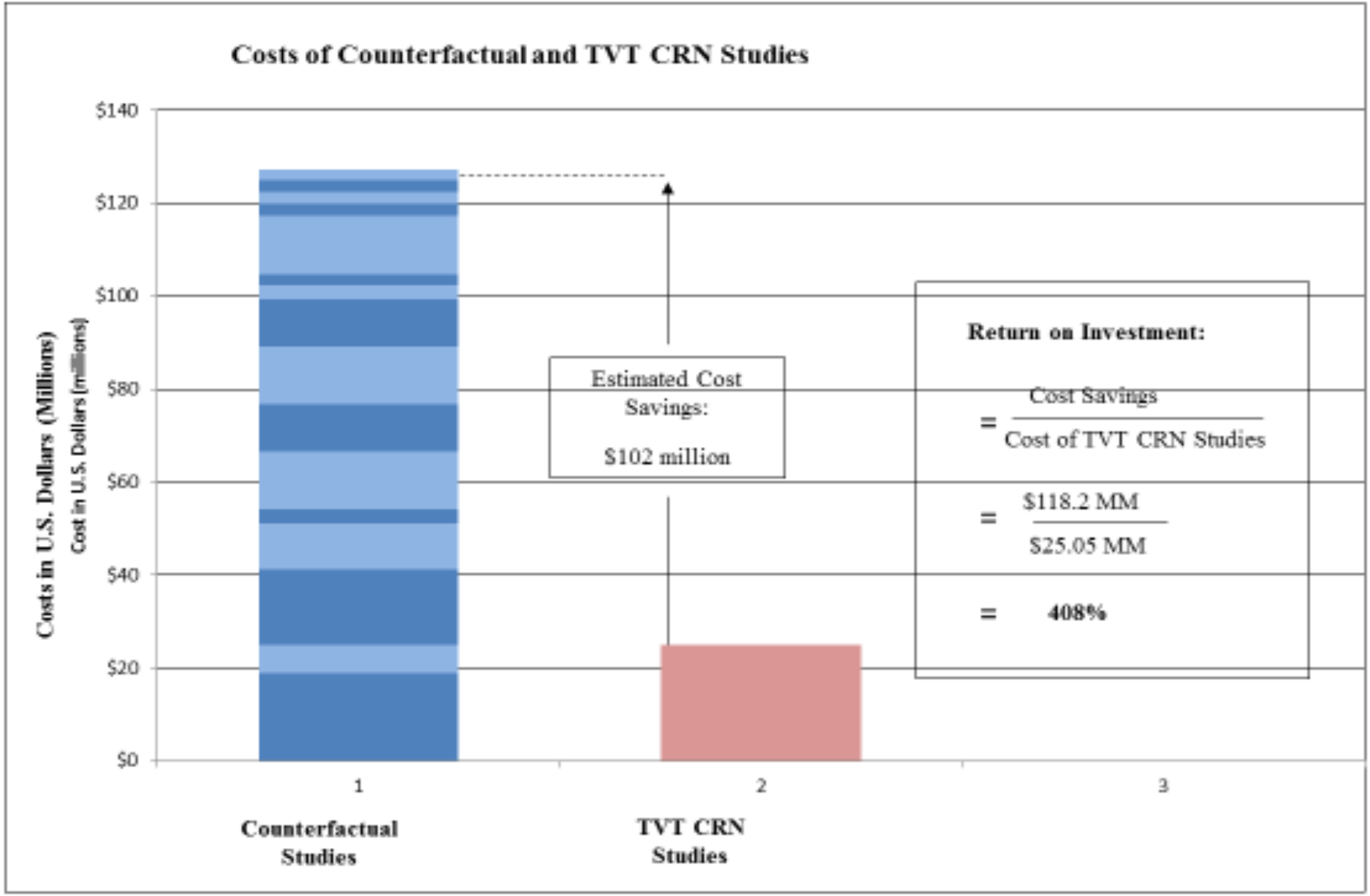
- ROI = (*Cost Savings from Investment*)/ (*Cost of Investment*) * 100
- Cost Savings from Investment (CSI) = cost of traditional studies (CTS) over time period **minus** cost of investment (X)

Methods: days-saved metric

- The time period for measurement is the “evidence generation period”, the time from the first enrolled subject to the end of the study. We are calling this the real scenario time for evidence generation.
- Other time factors were excluded from the metric
  - Time for IRB varies broadly for different CRN and can be combined with other time intervals
  - Time for site enrollment could not be measured with FDA records and therefore introduces an underestimate into “days saved”.
- The counterfactual time for evidence generation is the rate of enrollment per cite, time the number of sites, time the study size plus the length of the study as specified by the design.
  - Rate of enrollment is taken from the pivotal study for the TVT that used traditional methods to enroll patient
- Days saved is then the difference between the real scenario time and the counterfactual time

Results: ROI

- TVT CRN was used to support 23 (pre-market and post-market) decisions submitted by three medical device companies were identified. In 21 studies.
- Three companies invested in TVT, funds given to ACC to conduct studies.
- The costs to these studies conducted in the TVT CRN is $25,050,000.
- The estimated costs of the counterfactual studies is a total of over $127 million using Resnic Model. ROI is estimated to be greater than 400%.
- Days saved vary among the studies conducted and reveal time savings from months to years.


Costs of Counterfactual and TVT CRN Studies
Costs in U.S. Dollars (Millions)
Cost in U.S. Dollars (millions)
$140
$120
$100
$80
$60
$40
$20
$0
Estimated Cost Savings:
$102 million
Return on Investment:
= Cost Savings / Cost of TVT CRN Studies
= $118.2 MM / $25.05 MM
= 408%
1
2
3
Counterfactual Studies
TVT CRN Studies

Results: ROI

- Cost of individual counterfactual studies vary between $2.2 to $18.9
- Total of the counterfactual studies = $127 million
- Cost of Investment (COI) = $25,050,000
- Cost Savings from Investment (CSI) = $127 million - $25,050,000
- = $102,171,539
- TVT Return on Investment (ROI) = (CSI/COI) * 100
- = ($102 million /25,050,000) * 100
- = 408%

Results: Days-saved

Study	Study Type	Total Counterfactual study time (days)	Real scenario - Days specified by design	Days Saved	Years Saved
A	PAS	4256	1825	2431	6.7
B	PAS	3756	1825	1931	5.3
C	Label Expansion	2001	1825	176	0.5
D	PAS	4810	1825	2985	8.2
E	Label expansion	2001	1825	176	0.5
F	PAS	3518	1825	1693	4.6
G	PAS	2164	1825	339	0.9
H	PAS	4482	3650	832	2.3
I	PAS	3460	1825	1635	4.5
J	PAS	4482	3650	832	2.3
K	PAS	2981	1825	1156	3.2
L	PAS	2878	1825	1053	2.9
M	PAS	2081	1825	256	0.7
M	PAS	2319	1825	494	1.4
O	PAS	2319	1825	494	1.4
P	PAS	1941	1825	116	0.3
Q	PAS	4379	3650	729	2.0
R	Label Expansion	610	365	245	0.7
S	PAS	1988	1825	163	0.4

Discussion: ROI Caveats

- Savings on evidence generation is not the only consideration for industry when considering use of CRN. Control over data is a factor that cannot be easily quantified in these metrics.
- Factors which drive under-estimation of this ROI
  - Combination of studies
  - Use model for PAS costs (Resnic et. al) knowing that label expansion studies cost more than PAS
  - Time required by staff to manage or monitor studies may be greater for traditional methods compared to CRN
  - Faster time to market contributes to financial benefit not included in this ROI (but reflected in days saved metric)
  - CRN provide a possible replacement for some MDR, future

Discussion: ROI

- What are the drivers of the savings?
  - Inherent savings – using claims data there was no need to conduct site-based follow-up of individuals for outcomes; faster enrollment with so many sites.
  - ***Leverage, reuse of data collected in registries for other purposes (e.g., quality control).
- The ROI for using registry for hospitals and healthcare systems is not addressed here
  - There is at least one study that calculates the benefit of registry use by hospitals
  - The Kaiser-Permanente registries more than pay for themselves. KP heavily uses its data to guide management of the system. (personal communication)

Discussion: Days-saved

- Days-saved may be an under estimate because our metric did not capture elimination of site enlisting.
- The meaning of days-saved differs for pre and post market studies.
- For the PAS, the days-saved is a measure of efficiency, but does not have an effect on the ROI.
- For label expansion studies the days-saved may translate to faster time to market. This would effect the ROI.
- Because timing for taking a product to market is a business decision, it may not be the same as days-saved. Also the ROI of faster time to market involves the size of the increased market due to the label expansion and the margin on a product.

Public health benefit

- Public health benefits of CRN include:
  - Larger study sized that capture heterogeneity in the population
  - Larger number of study sites capture heterogeneity among operators
  - CRN provides near real time surveillance, improving upon passive surveillance currently relied upon.
- The public health benefits of the CRN apply to all stakeholders.
- For the device manufactures the public health benefits translate to:
  - Faster potential recalls, and smaller recalls
  - Protection of brand and few recalls due to detection of problems early
  - Faster time to market means that live saving technology gets to patients faster

Conclusions:

- One case study can not be widely generalized. This paper demonstrates a methodology that may be useful for study of other cases and used to monitor RWE use overtime.

Next steps

- Case study of vascular devices (VQI CRN) is underway. This will provide getter insight by allowing a comparison of case studies and discussion of the drivers of ROI and time saving
- The metrics may be useful to the NESTcc as a tool to monitor RWE evidence generation. This was set out as a role of the Coordinating Center by the Planning Board.