INVESTED Vanguard Year: What Did We Learn About SMART IRB?

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The National Patient-Centered Clinical Research Network

INfluenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated heart failure (INVESTED)

Investigators:
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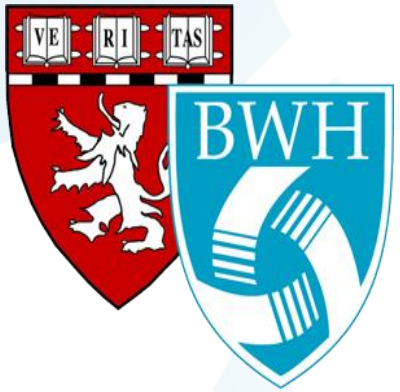

Funding:
National Heart, Lung and Blood Institute, ClinicalTrials.gov NCT02787044

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Impact of Influenza - United States

- Approximately 36,000 influenza-associated deaths during each influenza season, and over 200,000 influenza-related excess hospitalizations
- Patients with cardiovascular disease are at increased risk for influenza, and complications from influenza
- Influenza can trigger thromboembolic events and can be associated with myocardial depression
- Several analyses have documented an association between acute influenza infections and increased risk cardiovascular events, including ACS events and heart failure

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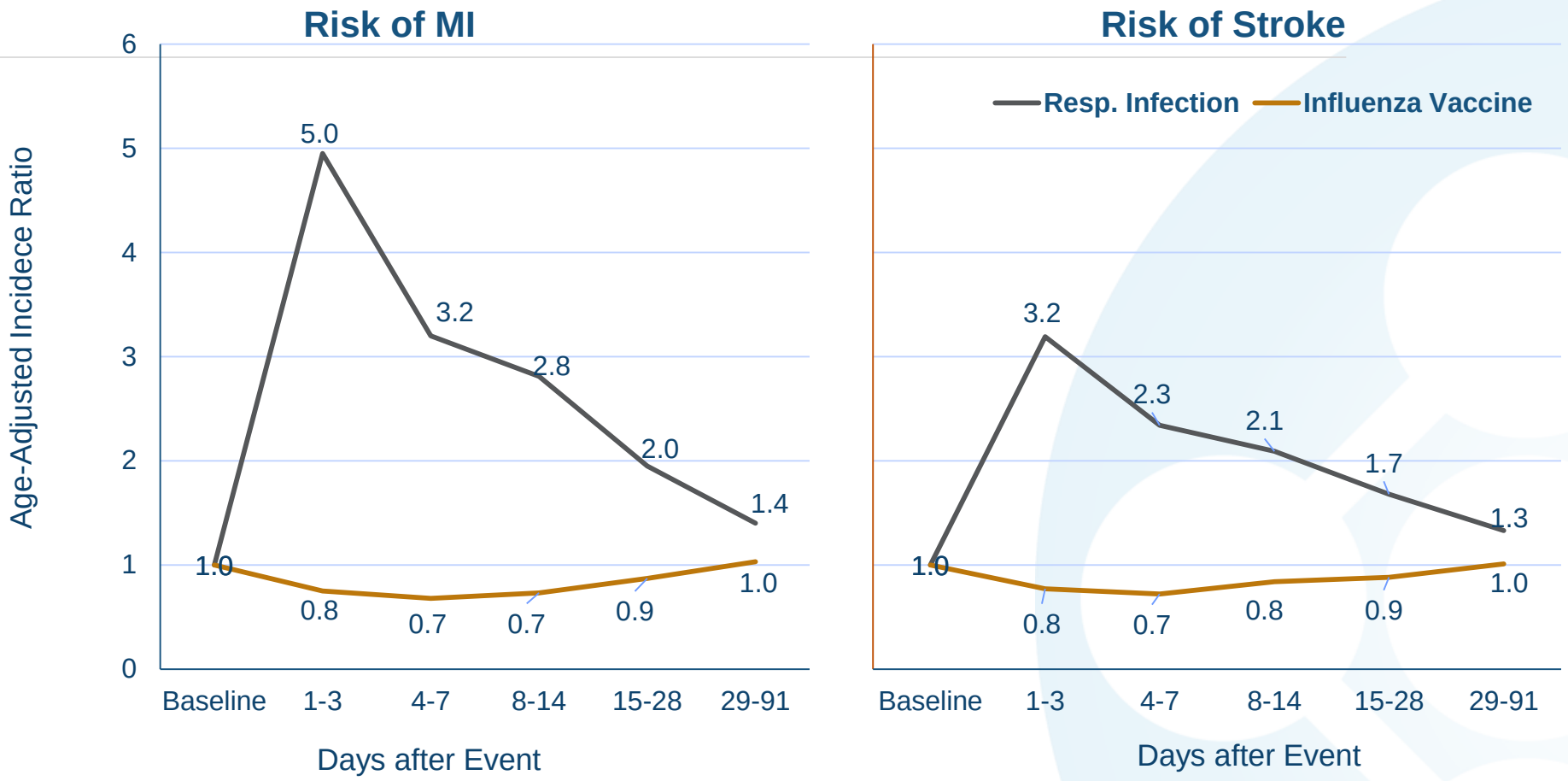
Thompson et al JAMA. 2003;289:179-186
Thompson et al JAMA. 2004;292:1333-1340
Madjid et al. EHJ 2007(28):1205-1210

Influenza Infections Trigger Cardiovascular Events



- Self-controlled case series study design – patients acted as their own control in periods when they were not exposed to when they are exposed to an influenza-like illness event
- UK General Practice Research Database: N = 20,486 first MI; N = 19,063 first stroke

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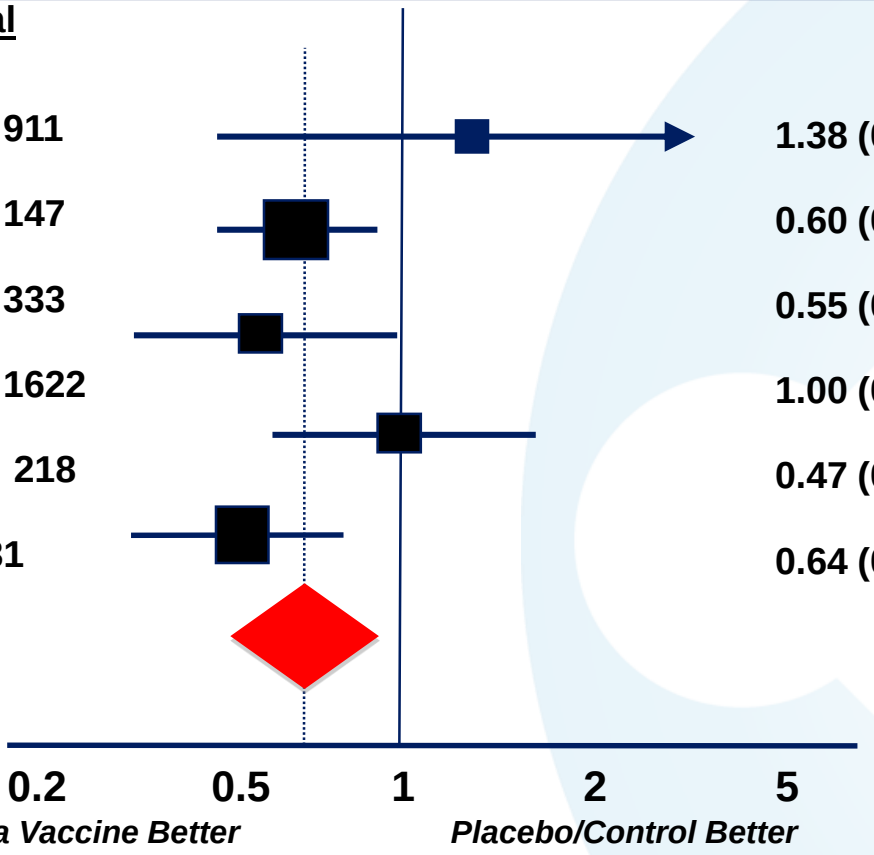
Smeeth L, et al. NEJM 2004;351(25):2611-8.

Influenza Vaccination Reduces CV Risk: A Meta-Analysis

Study	Influenza Vaccine Events	Influenza Vaccine Total	Placebo/ Control Events	Placebo/ Control Total	Risk Ratio (95% CI)
Govaert	7	927	5	911	1.38 (0.44 – 4.32)
FLUVACS	32	145	54	147	0.60 (0.41 – 0.87)
FLUCAD	16	325	30	333	0.55 (0.30 – 0.98)
DeVilliers	20	1620	20	1622	1.00 (0.54 – 1.85)
Phrommintikul	20	221	42	218	0.47 (0.29 – 0.77)
Total	95	3238	151	3231	0.64 (0.48 – 0.86)
	2.93%		4.67%		



Absolute Risk Difference: 1.74%
Number Needed to Treat: 58

Test for Heterogeneity I^2=28%
Overall P-Value = 0.003

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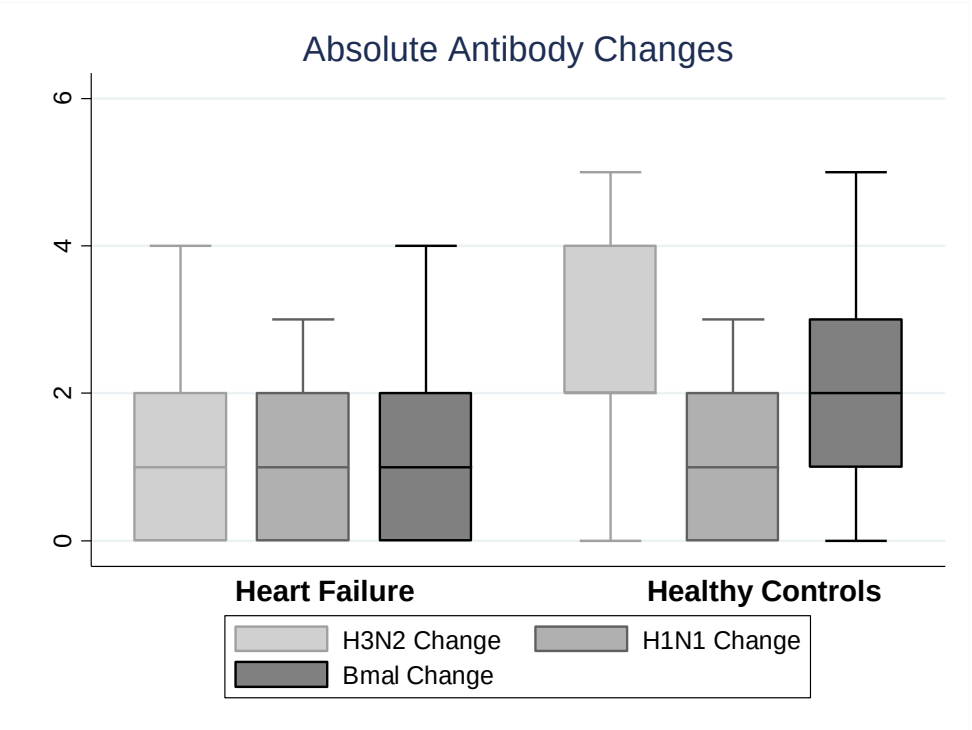
Udell JA, Zawi R, Bhatt DL et al… Farkouh ME, Cannon CP. JAMA 2013:310; 1711-1720.

Patients with Heart Failure Exhibit *Reduced Immune Response* to Vaccine that can be *Overcome with a Higher Dose* of Vaccine

Reduced Ab Response in HF Patients



Vardeny et al. J Card Fail 2009;15:368-373

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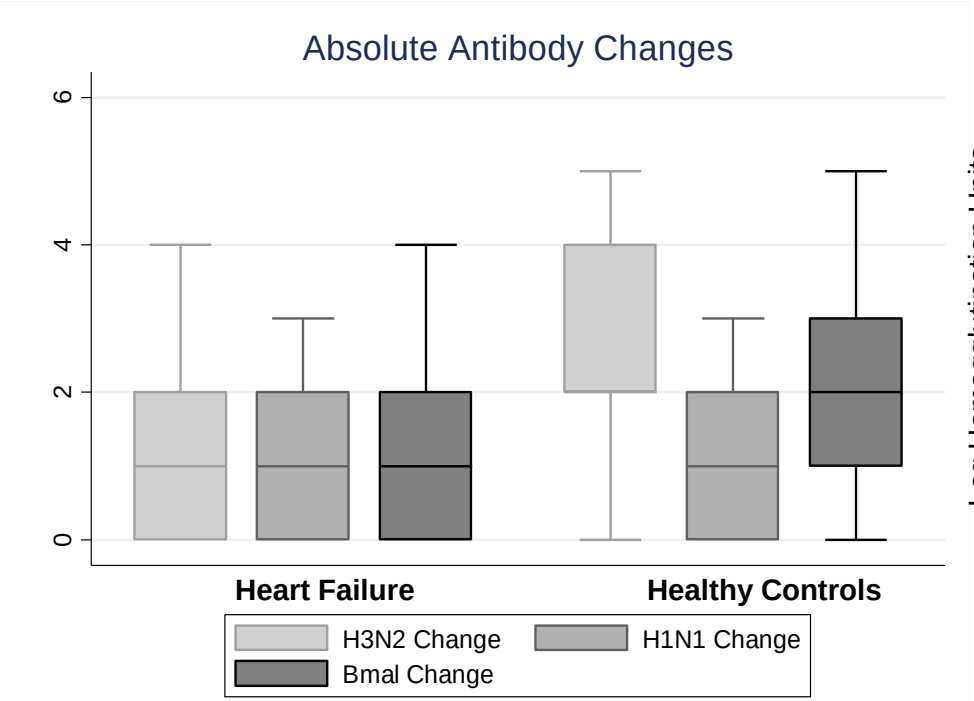
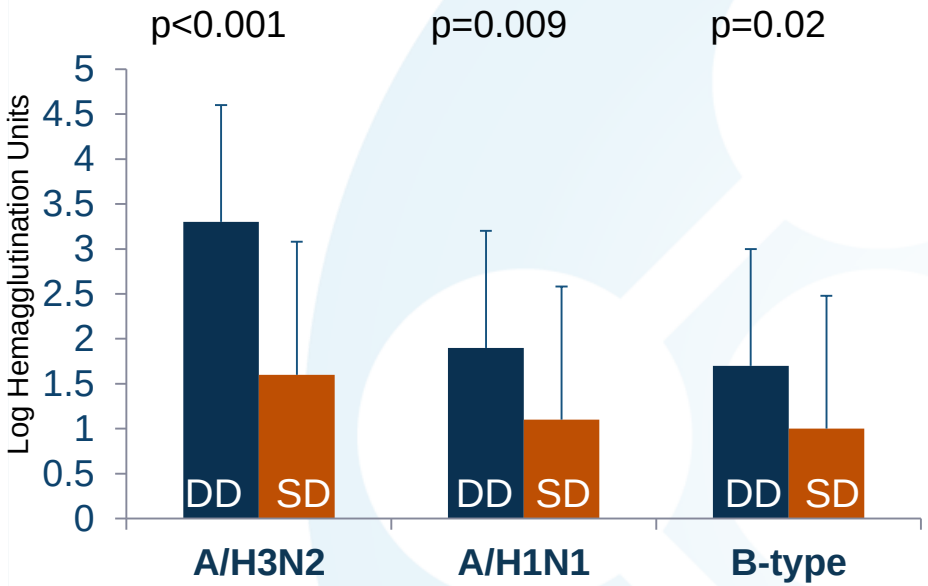
Patients with Heart Failure Exhibit *Reduced Immune Response* to Vaccine that can be *Overcome with a Higher Dose* of Vaccine

Reduced Ab Response in HF Patients



Vardeny et al. J Card Fail 2009;15:368-373

Increased Ab Titers with High Dose Vaccine



Pilot double-blind RCT of double dose (DD) vs. standard dose (SD) influenza vaccine

* Adjusted for baseline antibody titers

Vardeny et al. Eur J HF 2013;15(5):560-4

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Influenza Vaccine Preparations

- Influenza vaccine is an inactivated preparation
- Vaccine viral strains can change annually to reflect most commonly circulating strains in a given year (A/H1N1, A/H3N2, and B-type)
- Currently, there are trivalent and quadrivalent versions of the STANDARD dose (15 µg/strain) vaccine, and a trivalent version of a HIGH dose (60 µg/strain) vaccine

	Standard Dose	High Dose
Trivalent (2 A strains + 1 B strain)	✓ 15µg	✓ 60µg Approved for Medically Stable Individuals ≥ 65
Quadrivalent (2 A strains+ 2 B strains)	✓ 15µg	NO FORMULATION EXISTS

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Study Design Schema

INVESTED

NIH National Heart, Lung, and Blood Institute

Post-MI or HF Hospitalization

*with 1 additional CV risk factor
- age ≥ 65
- LVEF <40%
- DM
- BMI>30
- eGFR<60
- Hx ischemic stroke
- Hx PAD
- Current smoking

N = 9300

RANDOMIZED 1:1 DOUBLE BLIND ANNUAL VACCINE STRATEGY

All other CV Rx per treating MD

High Dose Trivalent Influenza Vaccine

Standard Dose Quadrivalent Influenza Vaccine

Followed up to 4 times a year with annual re-vaccination to assigned strategy

Duration
3 Influenza Seasons
+ Vanguard Season

Primary EP
Death or Cardiopulmonary Hospitalization

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VANGUARD (2016-2017) and Subsequent Years

- Began enrollment September 21, 2016
- Enrollment N=494, 39 sites
  - Canada: 13 VA: 9
  - PCORnet: 9 Midwest: 7-8
- Robust ancillary study opportunities including blood collection on ~1000-3000 patients
- 3 additional influenza Seasons
- www.investedtrial.org
  - Currently enrolling sites for second year

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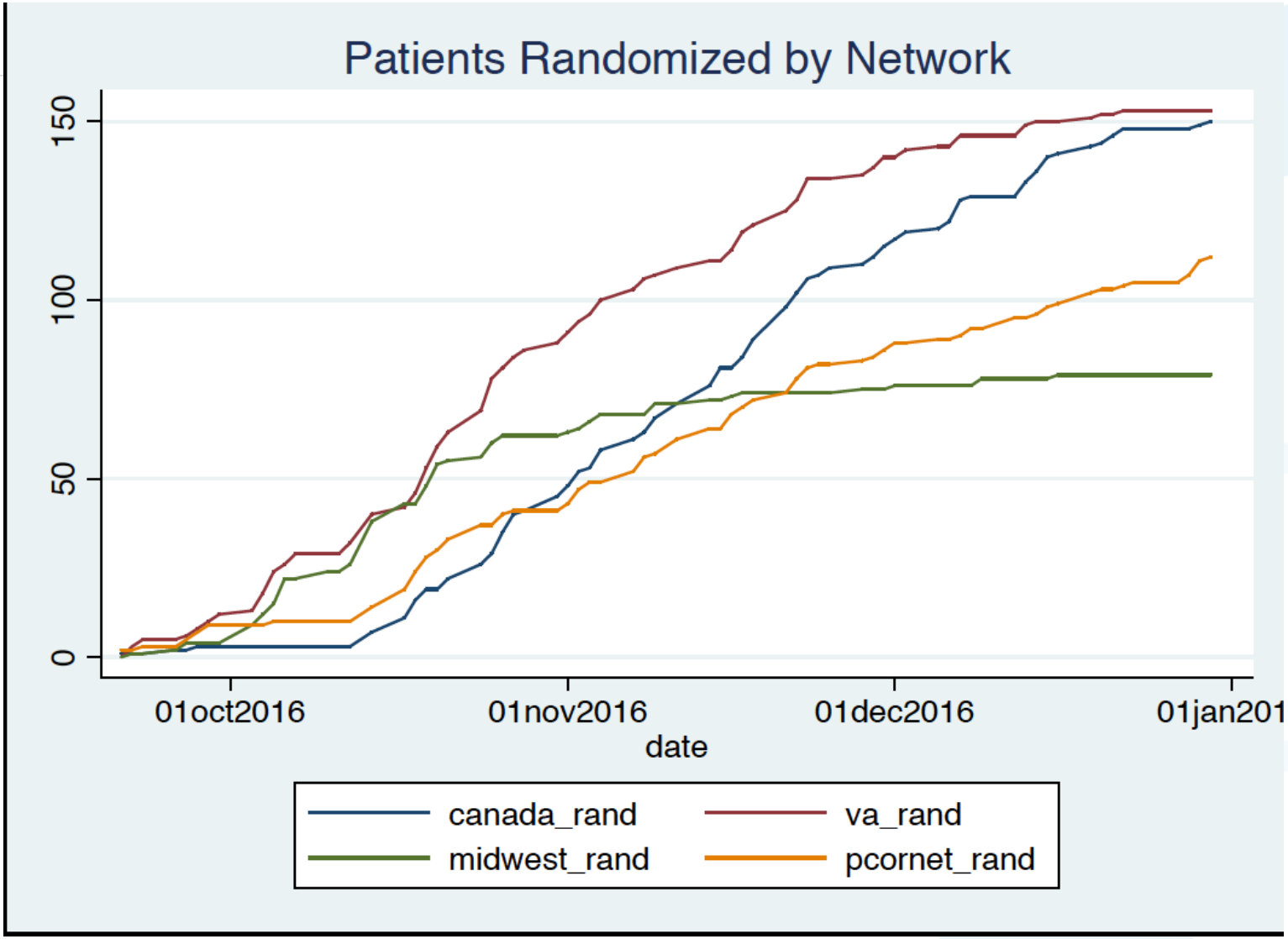
Vanguard Year



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Funding:
National Center for Advancing Translational Sciences (NCATS)

Grant Number: 3UL1TR001102-04S1

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What is SMART IRB?

- SMART IRB is an initiative developed under an award from the National Center for Advancing Translational Sciences ("NCATS") of the National Institutes of Health ("NIH") to support single Institutional Review Board ("IRB") review to facilitate multi-site human subjects research

- SMART IRB is not an IRB, but is a Master Common Reciprocal IRB Authorization Agreement that permits Participating Institutions to cede review of human subjects research to other Participating Institutions' IRBs
  - Lead site
  - Ceding sites

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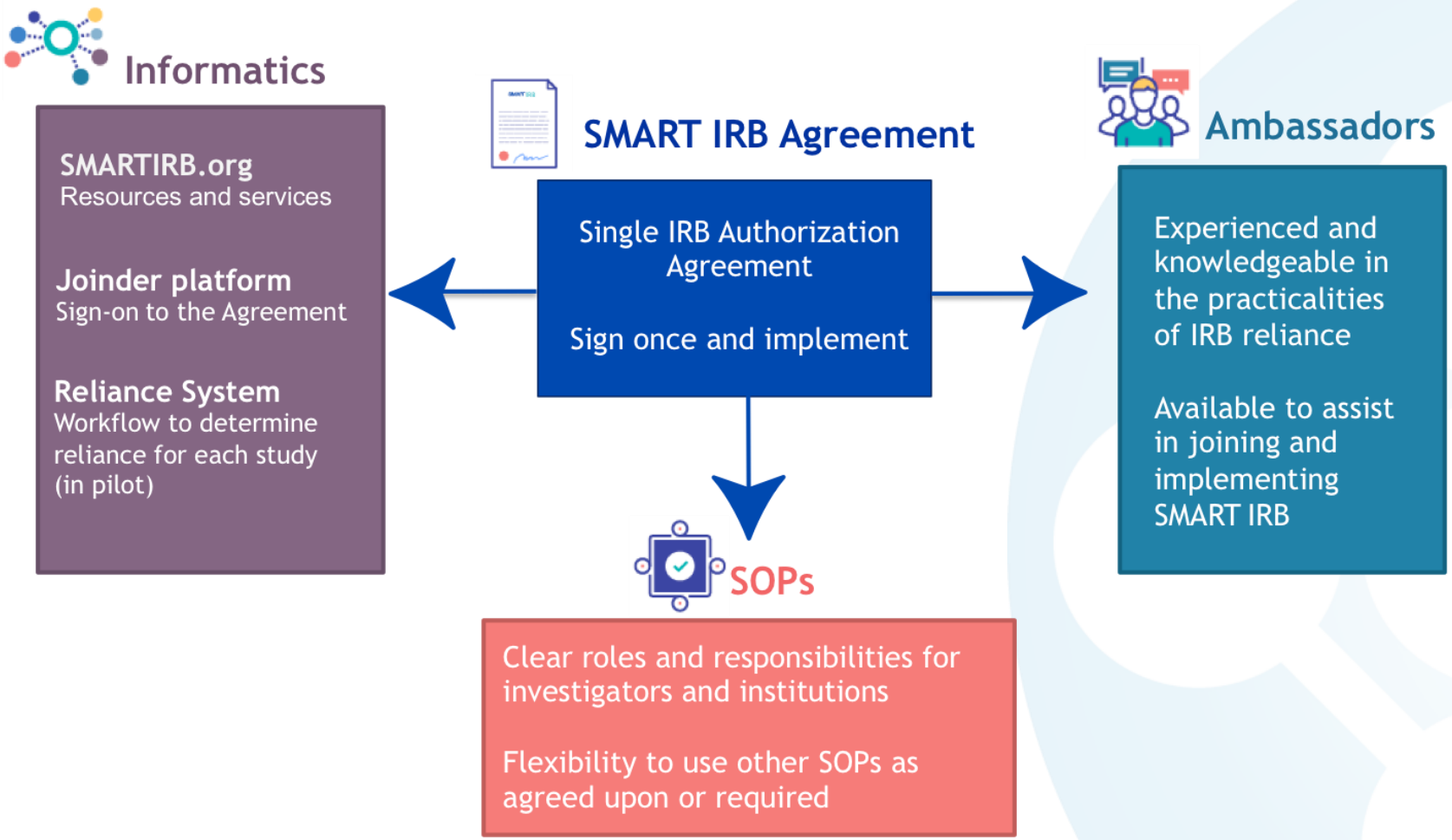
SMART IRB



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Why is SMART IRB Important to PCORnet?

- SMART IRB was created and implemented in response to the NIH's policy on Single IRB Review for Multi-Site Research (June 21, 2016)
- This policy will become effective on September 25, 2017 and applies to *"the domestic sites of NIH-funded multi-site studies where each site will conduct the same protocol involving non-exempt human subjects research, whether supported through grants, cooperative agreements, contracts, or the NIH Intramural Research Program*."
- PCORnet has encouraged all its sites to join SMART IRB, while harmonizing efforts with NCATS to implement this policy

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SMART IRB Evaluation

Approach to Single IRB Evaluation

- The PCORnet Coordinating Center worked in conjunction with the University of Wisconsin-Madison Health Science IRB and the INVESTED study team to conduct the evaluation of SMART IRB
- The evaluation will guide the continued implementation of the Single IRB model within PCORnet and may inform SMART IRB as well
- The evaluation focused on three key domains:
  - Efficiency
  - Resource use
  - User perception

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Timeline

- August 2016
  - PCORnet Coordinating Center (CC) collected initial metrics from all participating entities (ceded sites, non-ceded, lead site, and Reviewing IRB/OCT)
- Sept. - Dec. 2016
  - CC collected monthly metrics from participating entities
- December 2016
  - CC collected user perceptions from participating entities
- Jan. - Feb. 2017
  - CC completed quantitative and qualitative analysis
  - Final results expected late Feb. 2017
- Mar 2017
  - Results to be finalized

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INVESTED Sites and SMART IRB

- 14 of 15 participating PCORnet sites ceded review during INVESTED Vanguard year

Type of Site	Number of Sites
Ceded Sites	14 (13 of which have IRB approval)
Non-ceded Site	1
Lead Site	1 (University of Wisconsin at Madison)

- All data are from the INVESTED study's Vanguard year, August 2016 – December 2016.

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Time to Approval and First Enrollment

- Time to Approval for sites using SMART IRB/Ceding
  - Faster than non-ceding sites and academic standard
  - Slower than in CARRA *(note CARRA is registry vs INVESTED a trial)*

- First Enrollment for sites using SMART IRB/Ceding
  - Faster than non-ceding sites and academic standard --- by over 40 days!

	Ceded Sites		Non-Ceded Sites		
	INVESTED	CARRA	INVESTED	CARRA	Standard for Academic Medical Center[2]
Time from site package to IRB approval[1]	**80.8**	**61.4**	**121**	**143.7**	**103**
Time from site package to enrollment of first participant[1]	**126.3**	**-**	**149**	**-**	**169**

n=13

[1] Mean days

[2] Abbott D, Califf R, Morrison BW, Pierre C, Bolte J, Chakraborty S. Cycle time metrics for multisite clinical trials in the United States. *Therapeutic Innovation and Regulatory Science;* 2013; 47(2) 152-160.

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Cost Incurred by Ceded Sites for Initial Review

- Median cost per Ceding Site = **$1,495** ($560+ $935) VS. Estimated Cost if had not Ceded = $900
- Total estimated cost for INVESTED Ceding sites = **$20,930**
- Expect costs to decrease, as more time than usual was spent in learning about ceding process, making decision to cede, and navigating the process

Costs	Mean Number of Hours	Median Number of Hours	Range Number of Hours	Mean Hourly Rate	Median Hourly Rate	Range Hourly Rate	Sites' Median Cost of Ceding Review
Estimated Time and Cost of Determination to Cede	9.7	8.0	2.5 - 27.5	$63	$70	$32 - $96	$560
Estimated Time and Cost of Providing Local Context to Ceding IRB	23.8	11.0	1 - 80	$64	$45	$32 - $109	$935
Estimated Time and Cost of Preparation for Local IRB Review, If Choosing **Not** to Cede	17.0	15.0	3 - 80	$54	$45	$23 - $109	$900

n=9

Median costs

Cost Incurred by Ceded Sites for Additional IRB Activity (Amendments)

- To date, the median cost of IRB activity for ceded sites is minimal ($432), but only 7 sites reported modifications
  - Extrapolated across all sites, estimated cost for modifications in a study similar to INVESTED is **$864**
  - All modifications were minor (adding personnel, revising documents)
- More data are needed to evaluate IRB activity for one full year.

IRB Activity	October	November	December	Total Cost
Amendments Submitted by Ceded Sites	$216	$216	$0	**$432**

n=7

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Cost Incurred by Non-Ceded Sites

- Only one site chose to maintain local IRB review. More data are needed to perform a comparative analysis.

	Mean Number of Hours	Mean Hourly Rate	Total Cost
Estimated time and cost required at local institution to prepare and obtain initial IRB approval	15	$23	$345

n=1

Cost Incurred by Lead Site for Initial Review

- Total estimated cost for INVESTED Lead site's initial submission = **$3,584**

Lead Site Activity - Initial Submission	Median Cost	Total Cost
Cost of Office of Clinical Trials (OCT) to Prepare the Template Consent Form	$64	$896
Cost of Finalizing the Protocol, after the Approval by the Executive Committee, for Submission to the IRB	$192	$2,688
Total	**$256**	**$3,584**

n=13

Median costs

Cost Incurred by Lead Site for Additional IRB Activity (Amendments)

- The median cost of IRB activity for the lead site additional review is **$672**, but only 10 sites reported modifications
  - Extrapolated across all sites, estimated cost for modifications in a study similar to INVESTED is **$941**

Lead Site Activity - Additional Activities Related to Single IRB Review	August	September	October	November	December	Total Cost
Cost of Additional Staff Time for Activities Directly Related to Single IRB Review	$544	$0	$128	$0	$0	$672

n=10

Median costs

Cost Incurred by Reviewing IRB

- Total $6,942, over five months

IRB Activity	Number of Hours	Hourly Rate	Cost
Educating and preparing the lead study team and relying site IRBs, and advising IRB review staff (IRB staff time)	48	$54	$2,600
Initial review of the study (IRB staff time)	34	$44	$1,500
Initial review of the study, including primary reviewer preparation and committee discussion (IRB committee time)	3	$767	$2,300
Changes of protocol to add sites (IRB staff time)	7.5	$43	$325
Changes of protocol for other ceded site changes (IRB staff time)	5	$43	$217
Total	**97.5**	**$952**	**$6,942**

N=1 entity (IRB), which reported on 14 sites

Total Cost

- Estimated total costs for pioneering early use of SMART IRB in INVESTED across 13 ceded sites = **$33,261**
- Cost incurred by 1 non-ceded site is $345

Cost Incurred by Using Single IRB Model	Total Based on Median
Cost Incurred by Ceded Sites for Initial Review	$20,930
Cost Incurred by Ceded Sites for Additional IRB Activity (Amendments; estimated)	$864
Cost Incurred by Lead Sites for Initial Review	$3,584
Cost Incurred by Lead Sites for Additional IRB Activity (Amendments; estimated)	$941
Cost Incurred by Reviewing IRB	$6,942
Total	**$33,261**

n=13

Median costs

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Satisfaction

- At the end of the study period, 50% of team members reported being Satisfied with the SMART IRB experience
- Most (44%) were also Satisfied with the new division of responsibilities

	Percent of Respondents Reporting "Very Satisfied or Satisfied"	Percent of Respondents Reporting "Neither Satisfied nor Dissatisfied"	Percent of Respondents Reporting "Very Dissatisfied or Dissatisfied"
Overall Satisfaction of SMART IRB	50%	25%	25%
Satisfaction with Division of Responsibilities	44%	31%	25%

n=16

Effect on Workload

- Majority (75%) reported an Increased Workload

	Decreased	Unchanged	Increased
Effect of SMART IRB on Workload (Decreased, Unchanged, Increased)	0%	25%	75%

n=16

“It’s not more or less work, but different work”

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Reported Benefits

- Improved document tracking/management
  - Greater confidence that all sites are using the right versions
- Enhanced consistency in study conduct across sites
- Enhanced communication and collaboration
- Decreased site implementation time overall
- Satisfaction with the SMART IRB Agreement having flexible and complete terms

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Reported Challenges

- Changes at local sites in recruitment strategies increased IRB review and start up time
- Addition and removal of site personnel was time-consuming for all parties
- Education of study teams regarding the single IRB process required extra time for all parties
- Creation of individual accounts to access Reviewing IRB submission system required extra time on the part of the lead site
- Collection and review of local information provided in ceded site surveys required extra time for all parties

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Reported Local Barriers

- Culture
  - Some sites required local IRB even when they had ceded review
  - Some sites reluctant to use standard consent and HIPAA language…more comfortable with what they have always used
- State laws and the collection of SSNs
- Knowing who is considered “engaged in research” at the local level
- Disclosure of Conflict of Interest (COI)

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Suggestions for the Future

- Ensure lead and ceding sites are clear on their own IRB's requirements around Single IRB
- Be clear on local requirements in beginning
  - Determine what provisions will be made around local requirements
- Provide extra resources for lead study team, especially if new to SMART IRB
  - Education and funding
  - It is a new role for them and they may rely more heavily on the reviewing IRB for guidance
- Try to avoid full local reviews for ceding sites
  - Duplicative and adds time
- Start early to onboard sites

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Summary

- Faster time to IRB approval and enrollment of first participant
- Overall satisfaction
- Single IRB model will need further evaluation, acquiring additional data to further explore its efficiency, cost, and user perception
- **Culture change takes time and perseverance**

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