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

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

Investigators:
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Scott Solomon, MD

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

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

Influenza Vaccination Reduces CV Risk: A Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Influenza Vaccine Events</th>
<th>Placebo/Control Events</th>
<th>Total Events</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Govaert</td>
<td>7</td>
<td>5</td>
<td>911</td>
<td>1.38 (0.44 – 4.32)</td>
</tr>
<tr>
<td>FLUVACS</td>
<td>32</td>
<td>54</td>
<td>147</td>
<td>0.60 (0.41 – 0.87)</td>
</tr>
<tr>
<td>FLUCAD</td>
<td>16</td>
<td>30</td>
<td>333</td>
<td>0.55 (0.30 – 0.98)</td>
</tr>
<tr>
<td>DeVilliers</td>
<td>20</td>
<td>20</td>
<td>1622</td>
<td>1.00 (0.54 – 1.85)</td>
</tr>
<tr>
<td>Phrommintikul</td>
<td>20</td>
<td>42</td>
<td>218</td>
<td>0.47 (0.29 – 0.77)</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>151</td>
<td>3231</td>
<td>0.64 (0.48 – 0.86)</td>
</tr>
</tbody>
</table>

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

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

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

![Graph showing absolute antibody changes in HF patients and healthy controls for H3N2, H1N1, and Bmal changes.](image)

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**

<table>
<thead>
<tr>
<th>Heart Failure</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>H3N2 Change</td>
<td>H1N1 Change</td>
</tr>
<tr>
<td>Bmal Change</td>
<td></td>
</tr>
</tbody>
</table>

**Increased Ab Titers with High Dose Vaccine**

- A/H3N2: \( p<0.001 \)
- A/H1N1: \( p=0.009 \)
- B-type: \( p=0.02 \)


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

* Adjusted for baseline antibody titers

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

<table>
<thead>
<tr>
<th></th>
<th>Standard Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trivalent</strong></td>
<td>✓ 15µg</td>
<td>✓ 60µg</td>
</tr>
<tr>
<td>(2 A strains +</td>
<td></td>
<td>Approved</td>
</tr>
<tr>
<td>1 B strain)</td>
<td></td>
<td>for</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medically</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Individuals ≥ 65</td>
</tr>
<tr>
<td><strong>Quadrivalent</strong></td>
<td>✓ 15µg</td>
<td>NO FORMULATION EXISTS</td>
</tr>
<tr>
<td>(2 A strains +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 B strains)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
INVESTED

Study Design Schema

Post-MI or HF Hospitalization

N = 9300

High Dose Trivalent Influenza Vaccine

Standard Dose Quadrivalent Influenza Vaccine

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

RANDOMIZED 1:1 DOUBLE BLIND ANNUAL VACCINE STRATEGY

All other CV Rx per treating MD

Duration
3 Influenza Seasons + Vanguard Season

Primary EP
Death or Cardiopulmonary Hospitalization

*with 1 additional CV risk factor

age ≥ 65
LVEF <40%
DM
BMI >30
eGFR <60
Hx ischemic stroke
Hx PAD
Current smoking

PCORnet
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
Vanguard Year

Patients Randomized by Network

- canada_rand
- va_rand
- midwest_rand
- pcornet_rand
Funding:
National Center for Advancing Translational Sciences (NCATS)
Grant Number: 3UL1TR001102-04S1
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
SMART IRB Agreement

  - Sign once and implement

SOPs

- Clear roles and responsibilities for investigators and institutions
- Flexibility to use other SOPs as agreed upon or required

Informatics

- SMARTIRB.org
  - Resources and services
- Joinder platform
  - Sign-on to the Agreement
- Reliance System
  - Workflow to determine reliance for each study (in pilot)

Ambassadors

- Experienced and knowledgeable in the practicalities of IRB reliance
- Available to assist in joining and implementing SMART IRB
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.
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
Timeline

August 2016
- PCORnet Coordinating Center (CC) collected initial metrics from all participating entities (ceded sites, non-ceded, lead site, and Reviewing IRB/OCT)

- 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
### INVESTED Sites and SMART IRB

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

<table>
<thead>
<tr>
<th>Type of Site</th>
<th>Number of Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceded Sites</td>
<td>14 (13 of which have IRB approval)</td>
</tr>
<tr>
<td>Non-ceded Site</td>
<td>1</td>
</tr>
<tr>
<td>Lead Site</td>
<td>1 (University of Wisconsin at Madison)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Ceded Sites</th>
<th>Non-Ceded Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INVESTED</td>
<td>CARRA</td>
</tr>
<tr>
<td>Time from site package to IRB approval¹</td>
<td>80.8</td>
<td>61.4</td>
</tr>
<tr>
<td>Time from site package to enrollment of first participant¹</td>
<td>126.3</td>
<td>-</td>
</tr>
</tbody>
</table>

n=13
¹ Mean days
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

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

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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.

<table>
<thead>
<tr>
<th>IRB Activity</th>
<th>October</th>
<th>November</th>
<th>December</th>
<th>Total Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendments Submitted by Ceded Sites</td>
<td>$216</td>
<td>$216</td>
<td>$0</td>
<td>$432</td>
</tr>
</tbody>
</table>

n=7
Cost Incurred by Non-Ceded Sites

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

<table>
<thead>
<tr>
<th>Mean Number of Hours</th>
<th>Mean Hourly Rate</th>
<th>Total Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated time and cost required at local institution to prepare and obtain initial IRB approval</td>
<td>15</td>
<td>$23</td>
</tr>
</tbody>
</table>

n=1
Cost Incurred by Lead Site for Initial Review

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

### Median Costs

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

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.

<table>
<thead>
<tr>
<th>Lead Site Activity - Additional Activities Related to Single IRB Review</th>
<th>August</th>
<th>September</th>
<th>October</th>
<th>November</th>
<th>December</th>
<th>Total Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of Additional Staff Time for Activities Directly Related to Single IRB Review</td>
<td>$544</td>
<td>$0</td>
<td>$128</td>
<td>$0</td>
<td>$0</td>
<td>$672</td>
</tr>
</tbody>
</table>

n=10

Median costs
# Cost Incurred by Reviewing IRB

**Total $6,942, over five months**

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

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

<table>
<thead>
<tr>
<th>Cost Incurred by Using Single IRB Model</th>
<th>Total Based on Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost Incurred by Ceded Sites for Initial Review</td>
<td><strong>$20,930</strong></td>
</tr>
<tr>
<td>Cost Incurred by Ceded Sites for Additional IRB Activity (Amendments; estimated)</td>
<td><strong>$864</strong></td>
</tr>
<tr>
<td>Cost Incurred by Lead Sites for Initial Review</td>
<td><strong>$3,584</strong></td>
</tr>
<tr>
<td>Cost Incurred by Lead Sites for Additional IRB Activity (Amendments; estimated)</td>
<td><strong>$941</strong></td>
</tr>
<tr>
<td>Cost Incurred by Reviewing IRB</td>
<td><strong>$6,942</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$33,261</strong></td>
</tr>
</tbody>
</table>

Median costs

n=13
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.

<table>
<thead>
<tr>
<th></th>
<th>Percent of Respondents Reporting “Very Satisfied or Satisfied”</th>
<th>Percent of Respondents Reporting “Neither Satisfied nor Dissatisfied”</th>
<th>Percent of Respondents Reporting “Very Dissatisfied or Dissatisfied”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Satisfaction of SMART IRB</td>
<td>50%</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>Satisfaction with Division of Responsibilities</td>
<td>44%</td>
<td>31%</td>
<td>25%</td>
</tr>
</tbody>
</table>

n=16
Effect on Workload

 Majority (75%) reported an Increased Workload

<table>
<thead>
<tr>
<th>Effect of SMART IRB on Workload (Decreased, Unchanged, Increased)</th>
<th>Decreased</th>
<th>Unchanged</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
<td>25%</td>
<td>75%</td>
</tr>
</tbody>
</table>

n=16

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