The MITIGATE Study: Insights from a Decentralized, Virtual, Electronic Health Record-Based Pragmatic Clinical Trial

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Cardiovascular and Metabolic Conditions Research Solution Through Technology and Advanced Analytics Research (STAR) Group
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NIH Collaboratory Grand Rounds: Rethinking Clinical Trials
Friday, June 18th 2021
MITIGATE is an investigator-initiated trial (IIT) funded by Amarin Corporation (Bridgewater, NJ)

We will be discussing the role of an FDA-approved drug, Vascepa®/Icosapent Ethyl (IPE), on risk of viral upper respiratory illness (URI)-related endpoints

However, use of IPE in this study is within the scope of the current product label/clinical practice guidelines
Background

- Patients with atherosclerotic cardiovascular disease (ASCVD) are at higher risk for viral URIs and associated complications.

- Randomized controlled trials of anti-viral strategies have largely focused on (1) moderate-severe viral URIs requiring hospitalization (with late enrollment) and (2) most investigational agents have been IV with potential safety or tolerability issues.
Several unmet needs in Coronavirus Disease 2019 (COVID-19) research:

- Enroll ASCVD patients in sufficient numbers into RCTs
- Focus on prevention in at-risk population in outpatient setting
- Test oral agents that are safe, tolerable, and widely available with direct anti-viral activity and anti-inflammatory pleiotropic effects
Rationale of Evaluating IPE

- **Vascepa®/Icosapent Ethyl (IPE)**
- Highly purified eicosapentaenoic acid (EPA)
- FDA-approved for primary and secondary prevention
- Safe and well-tolerated
- Putative anti-viral properties and known anti-inflammatory pleiotropic effects

CV death, non-fatal MI/stroke, UA

**REDUCE-IT Trial**

Rationale (Continued)

• VASCEPA COVID-19 CardioLink-9 trial (NCT04412018) enrolled 100 patients within 72 hours of a positive test result with ≥1 symptom(s) (i.e., fever, cough, sore throat, shortness of breath, and myalgia)

• Randomized 1:1 to IPE 4 g orally twice daily (loading) X 3 days followed by 2 g orally twice daily (maintenance) X 11 days vs. control

Bhatt DL et al. NLA 2020 Late Breaking Presentation (Unpublished Data)
Rationale (Continued)

• 25% within-group reduction in high-sensitivity C-reactive protein (hs-CRP) consistent with established anti-inflammatory effects of IPE

• Improvement in overall and domain-specific symptoms as assessed using influenza patient-reported outcome (FLU-PRO) score

Bhatt DL et al. NLA 2020 Late Breaking Presentation (Unpublished Data)
Rationale (Continued)

- **Limitations**: modest sample size, unblinded and uncontrolled (no placebo) design, and underpowered for clinical events

- PREPARE-IT-1/2 trials ([NCT04460651](https://clinicaltrials.gov/ct2/show/NCT04460651)) are currently investigating the role of IPE for prevention of COVID-19 in at-risk workers and for treatment of symptomatic COVID-19 in the general population

Bhatt DL *et al.* NLA 2020 Late Breaking Presentation (Unpublished Data)
Pragmatic Randomized Trial of Icosapent Ethyl for High-Cardiovascular Risk Adults
Objective

To evaluate the real-world clinical effectiveness of pre-treatment with IPE compared to usual standard of care to prevent or reduce the sequelae of laboratory-confirmed viral URI-related morbidity and mortality in patients with ASCVD.
Study Team

Alan S. Go, MD
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Co-Principal Investigator

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Data Consultant

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Research Coordinator

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Co-Investigator

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Co-Investigator

Van Selby, MD
Co-Investigator

Anne Goh, MD, MPH
Co-Investigator

Jesse Fitzpatrick, MD
Co-Investigator

Jacek Skarbinski, MD
Co-Investigator
Study Overview

MITIGATE Study
Virtual (EHR-Based), Randomized, Open-Label, Pragmatic Clinical Trial

Cohort Eligibility Criteria
- Age ≥50
- Established ASCVD
- No prior history of confirmed COVID-19
- Registered e-mail address at kp.org (eConsent)
- Not institutionalized or receiving palliative care
- No known life-limiting diagnoses

Target Enrollment and Follow-Up
16,500 (1,500 IPE and 15,000 controls)

Usual Care

10:1 Pre-Randomization
Stratified by age and respiratory status

IPE Intervention
0M ≥6M

Primary Outcomes
- Moderate-severe confirmed viral URIs
- Worst clinical status due to confirmed viral URI

Worst Clinical Status Ordinal Scale
1. Death
2. Hospitalized, Mechanical Ventilation (ECMO)
3. Hospitalized, High-Flow Supplemental O₂
4. Hospitalized, Low-Flow Supplemental O₂
5. Hospitalized, No Supplemental O₂
6. Urgent Care/ED Visit Only
7. No Relevant Clinical Encounters

PRECIS-2 Pragmatic CT Criteria

BMJ. 2015 May 8;350:h2147.
Eligibility

• **Pre-randomization:**
  - Randomizing eligible patients before the point of contact
  - Strategy of initial contact followed by informed consent
  - **Pros:** Maximizes generalizability, large passive control arm
  - **Con:** Requires high consent rate in intervention arm
Eligibility (Continued)

- **Operational criteria:**
  - Not a candidate for research
  - Ongoing care with a cardiologist
  - Documented telephone encounters
  - Age <75 years (after initial vaccine EUA)

- **Stratification variables:** service area, age, and prior lung disease status
### Inclusion Criteria
- Age $\geq 50$ years
- Informed consent
- No prior COVID-19
- Established ASCVD
- $\geq 12$ months continuous membership
- Registered e-mail in KP

### Exclusion Criteria
- Prior IPE
- Allergy
- Use of omega-3’s (stop)
- Pregnant
- On triple therapy
- Life-limiting diagnosis
## Eligibility (Continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention (N=3200)</th>
<th>IPE (N=1244)</th>
<th>Usual Care (N=32,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) Age, yrs</td>
<td>69.2 (9.1)</td>
<td>68.9 (8.8)</td>
<td>69.8 (9.1)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>1001 (31.3)</td>
<td>334 (26.8)</td>
<td>9954 (31.1)</td>
</tr>
<tr>
<td>Self-reported race, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2072 (64.8)</td>
<td>897 (72.1)</td>
<td>20,887 (65.3)</td>
</tr>
<tr>
<td>Black</td>
<td>211 (6.6)</td>
<td>67 (5.4)</td>
<td>2291 (7.2)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>468 (14.6)</td>
<td>124 (10.0)</td>
<td>4371 (13.7)</td>
</tr>
<tr>
<td>Multi-racial</td>
<td>153 (4.8)</td>
<td>59 (4.7)</td>
<td>1628 (5.1)</td>
</tr>
<tr>
<td>American Indian</td>
<td>19 (0.6)</td>
<td>6 (0.5)</td>
<td>155 (0.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>277 (8.7)</td>
<td>91 (7.3)</td>
<td>2668 (8.3)</td>
</tr>
<tr>
<td>Hispanic ethnicity, N (%)</td>
<td>302 (9.4)</td>
<td>100 (8.0)</td>
<td>3173 (9.9)</td>
</tr>
</tbody>
</table>

**Abbreviation:** yrs = years; IQR = interquartile range; N = number
## Eligibility (Continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention (N=3200)</th>
<th>IPE (N=1244)</th>
<th>Usual Care (N=32,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx cardiovascular disease, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1142 (35.7)</td>
<td>455 (36.6)</td>
<td>10,894 (34.0)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>1342 (41.9)</td>
<td>596 (47.9)</td>
<td>12,639 (39.5)</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>509 (15.9)</td>
<td>228 (18.3)</td>
<td>4722 (14.8)</td>
</tr>
<tr>
<td>Ischemic stroke/TIA</td>
<td>409 (12.8)</td>
<td>109 (8.8)</td>
<td>4703 (14.7)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>1020 (31.9)</td>
<td>366 (29.4)</td>
<td>10,666 (33.3)</td>
</tr>
</tbody>
</table>

**Abbreviation**: Hx = history and N = number
Recruitment to Intervention Arm

1. **Eligibility Review**
   - Upload to Appian
   - Send PCP Staff Message
   - If Provider Approves or Does Not Respond: Within two weeks of staff message, patient receives a recruitment email.
   - If Provider Declines: Patient is not recruited.

2. **Recruitment Email**
   - Download Eligible Patient List
   - Import Data
   - Send Recruitment Email with eConsent Link via REDCap

3. **Screening Call**
   - Screening Call
   - Real-Time eConsent Visit
   - Review eConsent
   - Scheduled eConsent Visit
## Recruitment

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Patient Status</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approval</strong></td>
<td>Approved</td>
<td>930 (29%)</td>
</tr>
<tr>
<td></td>
<td>No Response (&gt;2 weeks)</td>
<td>2030 (63%)</td>
</tr>
<tr>
<td></td>
<td>Awaiting approval (&lt;2 weeks)</td>
<td>200 (6%)</td>
</tr>
<tr>
<td></td>
<td>Refused/Ineligible</td>
<td>40 (1%)</td>
</tr>
<tr>
<td><strong>Screening</strong></td>
<td>Screening call attempted (N=2960)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consented to Study Drug</td>
<td>1244 (42%)</td>
</tr>
<tr>
<td></td>
<td>Declined Study Drug</td>
<td>988 (33%)</td>
</tr>
<tr>
<td></td>
<td>Ineligible</td>
<td>66 (2%)</td>
</tr>
<tr>
<td></td>
<td>Screening In Progress</td>
<td>662 (22%)</td>
</tr>
</tbody>
</table>

**Abbreviations**: N = number
## Recruitment

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Patient Status</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td>Time to first reached, days, median (IQR)</td>
<td>10 (5-19)</td>
</tr>
<tr>
<td></td>
<td>Time to consent, days, median (IQR)</td>
<td>17 (7-36)</td>
</tr>
<tr>
<td></td>
<td>Number of contacts, median (IQR)</td>
<td>5 (3-7)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>14,757</td>
</tr>
<tr>
<td></td>
<td>Phone (Reached)</td>
<td>6024 (41%)</td>
</tr>
<tr>
<td></td>
<td>Voicemail</td>
<td>3446 (23%)</td>
</tr>
<tr>
<td></td>
<td>Called (No message)</td>
<td>2759 (19%)</td>
</tr>
<tr>
<td></td>
<td>E-mail</td>
<td>2227 (15%)</td>
</tr>
<tr>
<td></td>
<td>Other (Text/Mailing)</td>
<td>301 (2%)</td>
</tr>
</tbody>
</table>

**Abbreviations:** N = number, IQR = interquartile range
# Recruitment Contacts by Role

<table>
<thead>
<tr>
<th>Role</th>
<th>Phone</th>
<th>Email</th>
<th>Text</th>
<th>Mailing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Physician</td>
<td>1050</td>
<td>494</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Research Coordinator</td>
<td>4236</td>
<td>1319</td>
<td>2</td>
<td>263</td>
</tr>
<tr>
<td>Research Nurse</td>
<td>6999</td>
<td>414</td>
<td>16</td>
<td>5</td>
</tr>
</tbody>
</table>

~15,000 recruitment calls (and ~7,000 follow-up calls) by 1 MD, 1-3 RNs, and 2-4 Research Coordinators
Recruitment

MITIGATE Study Cumulative Consents
Organization and Tools

**Electronic Health Record**
- Identify Eligible Patients
- Extract Baseline Data
- Send MD Staff Messages
- Follow-up for Outcomes

**Patient Tracking System**
- Business Process Management Platform
- Efficient Work Queues
- Schedule Tasks/Calls
- Document Communications
- Export E-Mail Lists

**eConsent Platform**
- Send Study Invitations with Direct Links and No Pre-Registration Steps
- Complete Informed Consent
- Send Completed eConsent
Flexibility – Drug Delivery

• Internal specialty pharmacy supports clinical trials for all 21 medical centers and coordinates with research teams and sponsors for:
  ✓ Study medication receipt and stocking
  ✓ Internal prescribing for initial script and refills
  ✓ Distribution via express shipping
  ✓ End-to-end tracking of study drug
# Flexibility – Adherence

<table>
<thead>
<tr>
<th>Follow-up and Adherence</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication not started, N (%)</td>
<td>26 (2%)</td>
</tr>
<tr>
<td>Medication discontinued, N (%)</td>
<td>94 (8%)</td>
</tr>
<tr>
<td>Due to patient preference</td>
<td>69 (73%)</td>
</tr>
<tr>
<td>Due to adverse event</td>
<td>25 (27%)</td>
</tr>
<tr>
<td>Reached minimum follow-up, N (%)</td>
<td>17 (1%)</td>
</tr>
<tr>
<td>Withdrawn from study, N (%)</td>
<td>4 (0.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Days on IPE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>116 (81)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>115 (45.5 to 183)</td>
</tr>
<tr>
<td>Range</td>
<td>0 – 287</td>
</tr>
</tbody>
</table>

**Abbreviations**: N = number, IPE = icosapent ethyl; SD = standard deviation; IQR = interquartile range
Flexibility – Adherence (Continued)

- Active
- Permanent Study Drug Discontinuation
- Censored

Follow-up Month

Number of Participants

1 2 3 4 5 6 7 8 9 10

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Follow-up

- Aggregate outcome data reviewed monthly
- Endpoints based on validated ICD-10 and CPT codes with support from other EHR data
- Deaths identified from EHR and state/national databases
- Minimum follow-up = 6 months
## Co-Primary Outcomes

**Median (IQR) follow-up time:** 107 (56-184) days  
**Follow-up duration:** 10,465 PY

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate-to-severe confirmed viral URIs</td>
<td>1.0 per 100 PY</td>
</tr>
<tr>
<td>Encounters without low SpO₂/supplemental O₂ requirement</td>
<td>1.4 per 100 PY</td>
</tr>
<tr>
<td>Positive lab tests only</td>
<td>3.9 per 100 PY</td>
</tr>
</tbody>
</table>

**Abbreviations:** IQR = interquartile range and PY = person-years

**Note:** To date, all viral URIs detected have been COVID-19 and appear robust based on blinded quality checks.
### Co-Primary Outcomes (Continued)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worst clinical status at any point in time:</td>
<td></td>
</tr>
<tr>
<td>1: Death</td>
<td>0.02%</td>
</tr>
<tr>
<td>2: Mechanically ventilated/extracorporeal membrane oxygenation</td>
<td>0.03%</td>
</tr>
<tr>
<td>3: High flow supplemental O₂</td>
<td>0.05%</td>
</tr>
<tr>
<td>4: Low flow supplemental O₂</td>
<td>0.15%</td>
</tr>
<tr>
<td>5: Hospitalized with no supplemental O₂</td>
<td>0.06%</td>
</tr>
<tr>
<td>6: Urgent Care or ED visit not leading to hospitalization</td>
<td>0.15%</td>
</tr>
<tr>
<td>7: No relevant clinical encounters</td>
<td>99.54%</td>
</tr>
</tbody>
</table>

**Abbreviations:** ED = emergency department
## Exploratory Outcomes

<table>
<thead>
<tr>
<th>Exploratory Endpoints</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>1.4 per 100 PY</td>
</tr>
<tr>
<td>MACE (3-point)</td>
<td>3.4 per 100 PY</td>
</tr>
<tr>
<td>Expanded MACE (5-point)</td>
<td>4.9 per 100 PY</td>
</tr>
<tr>
<td>Hospitalizations for worsening heart failure</td>
<td>2.2 per 100 PY</td>
</tr>
<tr>
<td>All-cause hospitalizations and ED visits</td>
<td>71.2 per 100 PY</td>
</tr>
</tbody>
</table>

**Abbreviations:** MACE = major adverse cardiovascular events; ED = emergency department; PY = person years
# Safety Outcomes

<table>
<thead>
<tr>
<th>Safety Endpoints</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident atrial fibrillation/flutter</td>
<td>1.5 per 100 PY</td>
</tr>
<tr>
<td>Hospitalization for atrial fibrillation/flutter</td>
<td>0.4 per 100 PY</td>
</tr>
<tr>
<td>Hospitalized bleeding event</td>
<td>1.1 per 100 PY</td>
</tr>
</tbody>
</table>

**Abbreviations**: PY = person years
Follow-up (Continued)

• Adverse events (AEs) leading to permanent study drug discontinuation and unexpected serious AEs (SAEs) are documented for the intervention arm only

• Reporting process for AEs/SAEs includes monthly follow-up calls (RN) + 24/7 study hotline and dedicated e-mail

• All reported AEs/SAEs are prospectively evaluated and confirmed by a study physician
AEs/SAEs Leading to Discontinuation

~2% of study participations experienced an AE/SAE leading to permanent discontinuation.
• Intention-to-treat (ITT) population = primary analysis
• Per-protocol population = subset receiving ≥1 dose
• Recurrent events included in all analyses
• Interaction analyses for age and pulmonary status
• All analyses adjusted for potential confounders
• MITIGATE adequately powered to detect a clinically meaningful difference between groups for actual event rates ≥10 events per 100 person-years

• Statistical assumptions change during a pandemic…
Limitations

• Pre-randomization requires a high consent rate and may bias the results towards the null hypothesis

• Open-label nature has the potential to introduce bias, though outcomes are objective and assessment is blinded
Limitations

• No face-to-face clinical encounters, but patients receive monthly contact and refills are centrally managed

• Findings are not necessarily generalizable to prevention in other at-risk groups nor the use of IPE as an active treatment for symptomatic COVID-19
Innovations

MITIGATE study represents several ‘firsts’ for RCTs in COVID-19 era…

- Enroll exclusively adults with established ASCVD
- Focus on prevention in at-risk population in outpatient setting
- Evaluate oral drug with known anti-inflammatory pleiotropic effects and potential anti-viral properties
- Employ an efficient, entirely remote/virtual design with no in-person contacts and low participant burden
Conclusions

• MITIGATE demonstrates feasibility of rapid, efficient decentralized recruitment of a diverse, real-world population for a protocol testing an intervention without the need for a complicated pre-existing or new clinical trial infrastructure.

• MITIGATE will clarify the role of pre-treatment with IPE in the prevention of URI-related morbidity and mortality in a high-risk cohort of patients with established ASCVD.
Acknowledgements

**Research RNs:**
Rachelle McEntee-Catap, RN
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Ria Rodriguez, MSN

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Verenice Tagle
Daren Huang
Harry Lee

A special thank you to our KPNC **members** and **providers**...
QUESTIONS?