MITIGATE STUDY

NIH Collaboratory Grand Rounds: Rethinking Clinical Trials

Friday, June 18th 2021

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

Andrew P. Ambrosy, MD **Alan S. Go, MD**

Cardiovascular and Metabolic Conditions Research
Solution Through Technology and Advanced Analytics Research (STAR) Group
Kaiser Permanente Northern California Division of Research

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Financial Disclosures

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

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Outline

- Background
- Rationale
- Study Overview
- Design Features
- Conclusions

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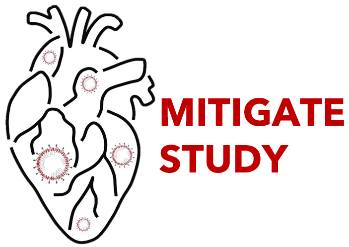
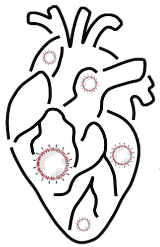


Background

- **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



Background (Continued)

- **Several unmet needs in Coronarvirus 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

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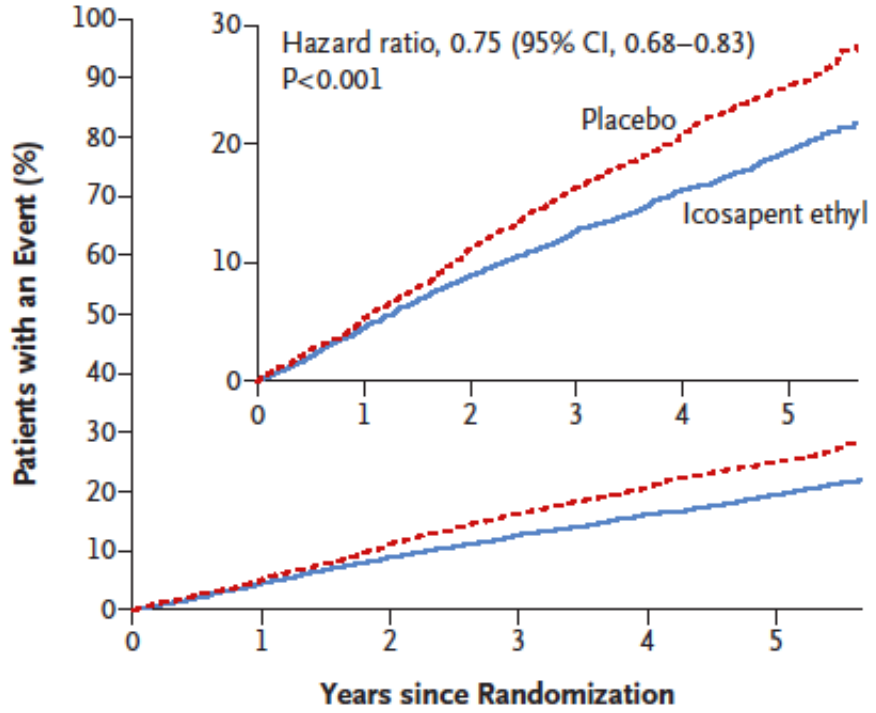
Rationale of Evaluating IPE

- 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

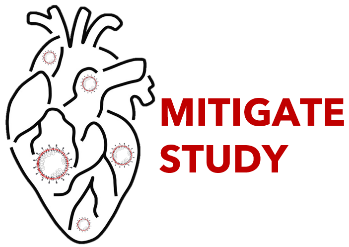
CV death, non-fatal MI/stroke, UA



No. at Risk						
Placebo	4090	3743	3327	2807	2347	1358
Icosapent ethyl	4089	3787	3431	2951	2503	1430

REDUCE-IT Trial

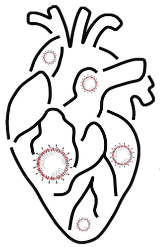
Bhatt DL *et al*. N Engl J Med. 2019 Jan 3;380(1):11-22.



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

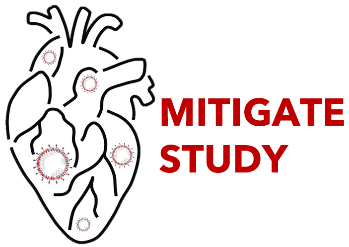
Bhatt DL *et al*. NLA 2020 Late Breaking Presentation (Unpublished Data)



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)

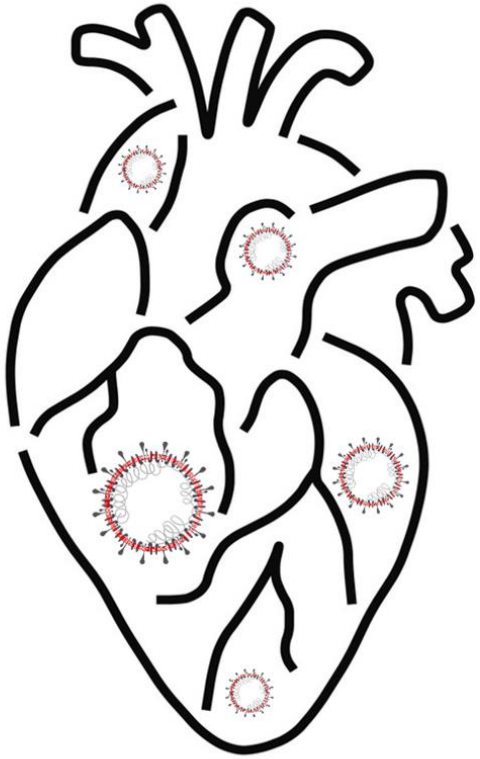


Rationale (Continued)

- **Limitations**: modest sample size, unblinded and uncontrolled (no placebo) design, and underpowered for clinical events
- PREPARE-IT-1/2 trials (**NCT04460651**) 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



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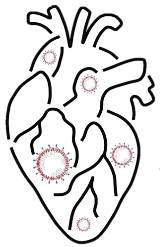

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Objective

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**

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Study Team

Alan S. Go, MD
Co-Principal Investigator

Andrew P. Ambrosy, MD
Co-Principal Investigator

Thida Tan, MPH
Sr. Project Manager

Rachel Thomas, RN
Research Nurse

Rishi Parikh, MPH
Data Consultant

Ryan Wi
Research Coordinator

Harshith Avula, MD, MPH
Co-Investigator

Matthew Solomon, MD, PhD
Co-Investigator

Van Selby, MD
Co-Investigator

Anne Goh, MD, MPH
Co-Investigator

Jesse Fitzpatrick, MD
Co-Investigator

Jacek Skarbinski, MD
Co-Investigator

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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 O_2
4	Hospitalized, Low-Flow Supplemental O_2
5	Hospitalized, No Supplemental O_2
6	Urgent Care/ ED Visit Only
7	No Relevant Clinical Encounters

Ambrosy AP *et al*. Am Heart J. 2021 Jan 28;235:54-64.

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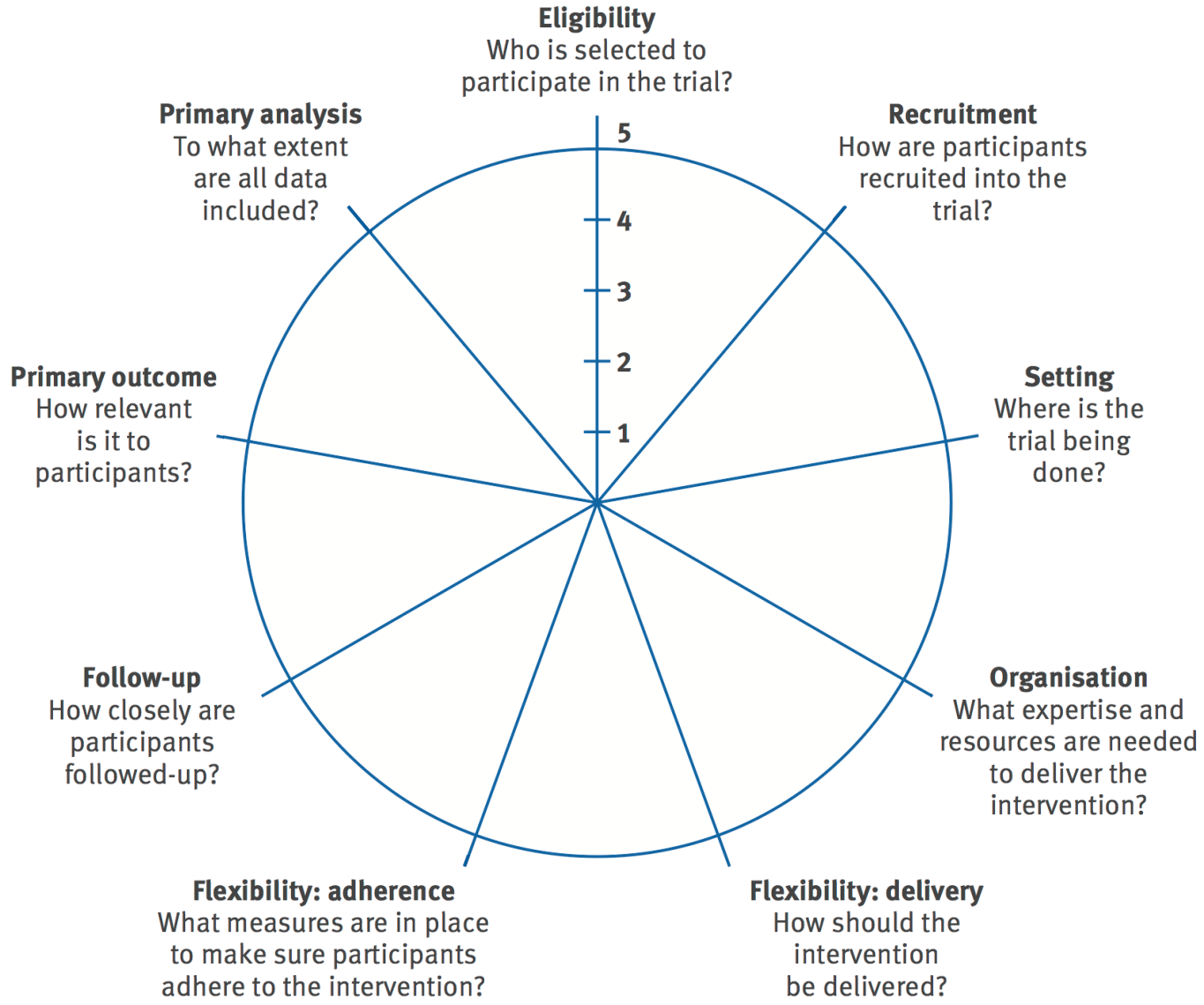
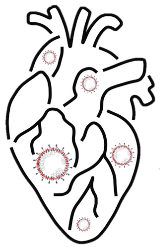
PRECIS-2 Pragmatic CT Criteria



BMJ. 2015 May 8;350:h2147.



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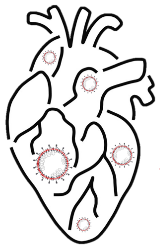
Eligibility

- **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



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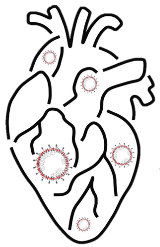
Eligibility (Continued)

- **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



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Eligibility (Continued)

Inclusion Criteria

- Age ≥50 years
- Informed consent
- No prior COVID-19
- Established ASCVD
- ≥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

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Eligibility (Continued)

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

Abbreviation: yrs = years; IQR = interquartile range; N = number

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Eligibility (Continued)

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

Abbreviation: Hx = history and N = number

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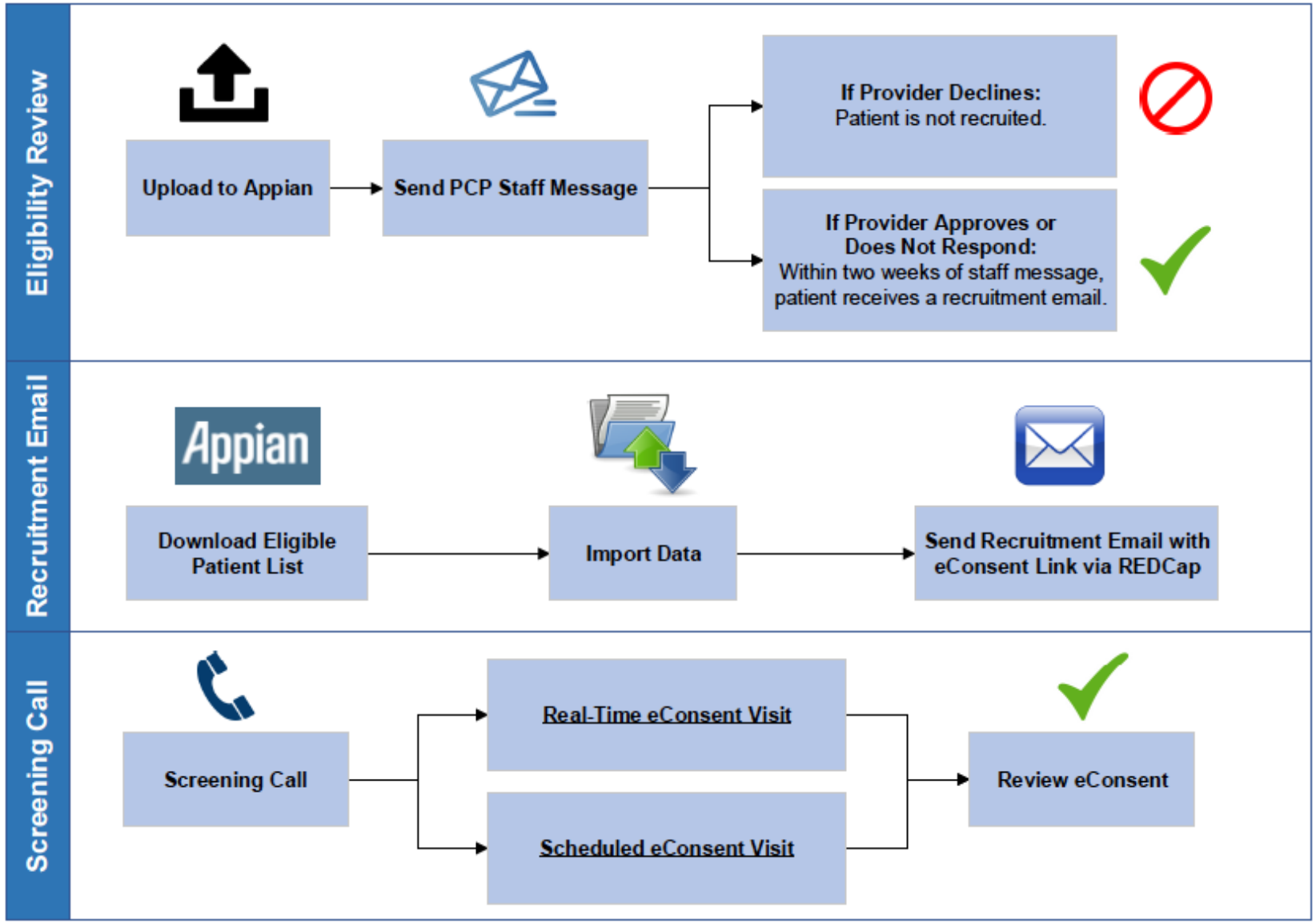
Recruitment to Intervention Arm



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Recruitment

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

Abbreviations: N = number

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Recruitment

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

Abbreviations: N = number, IQR = interquartile range

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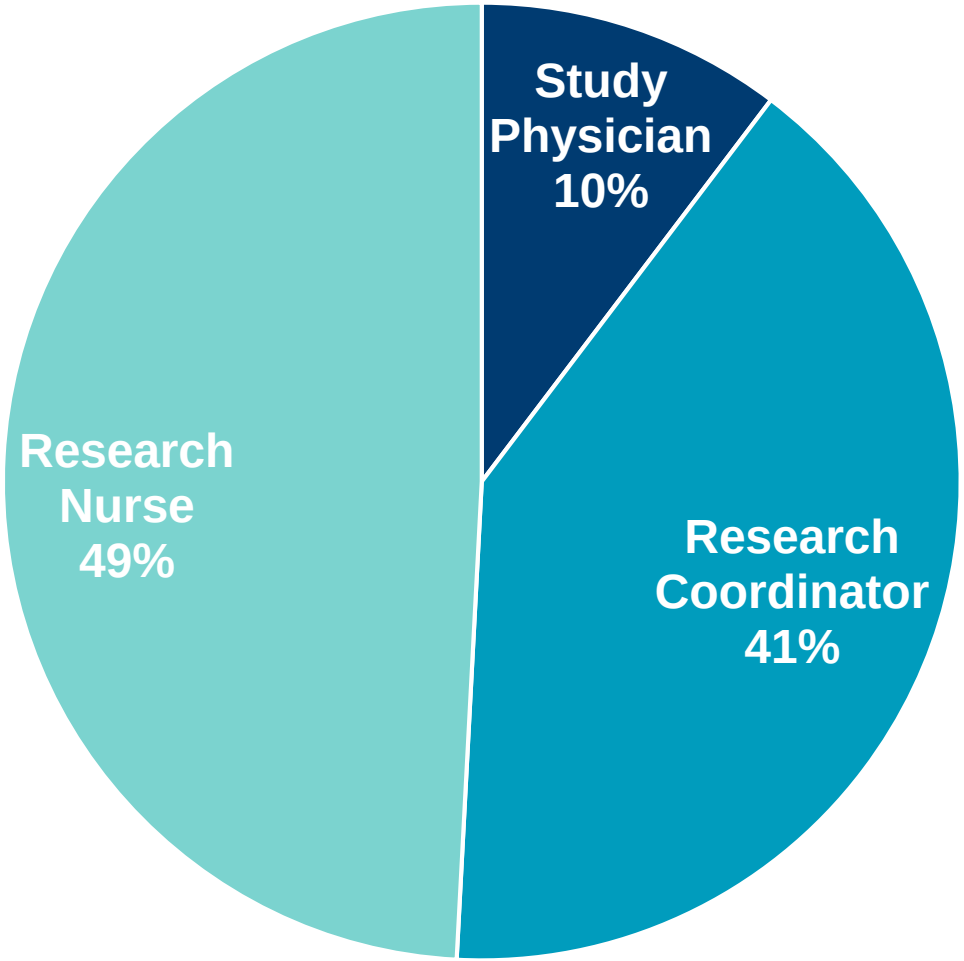
Recruitment Contacts by Role

Role	Phone	Email	Text	Mailing
Study Physician	1050	494	11	4
Research Coordinator	4236	1319	2	263
Research Nurse	6999	414	16	5



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

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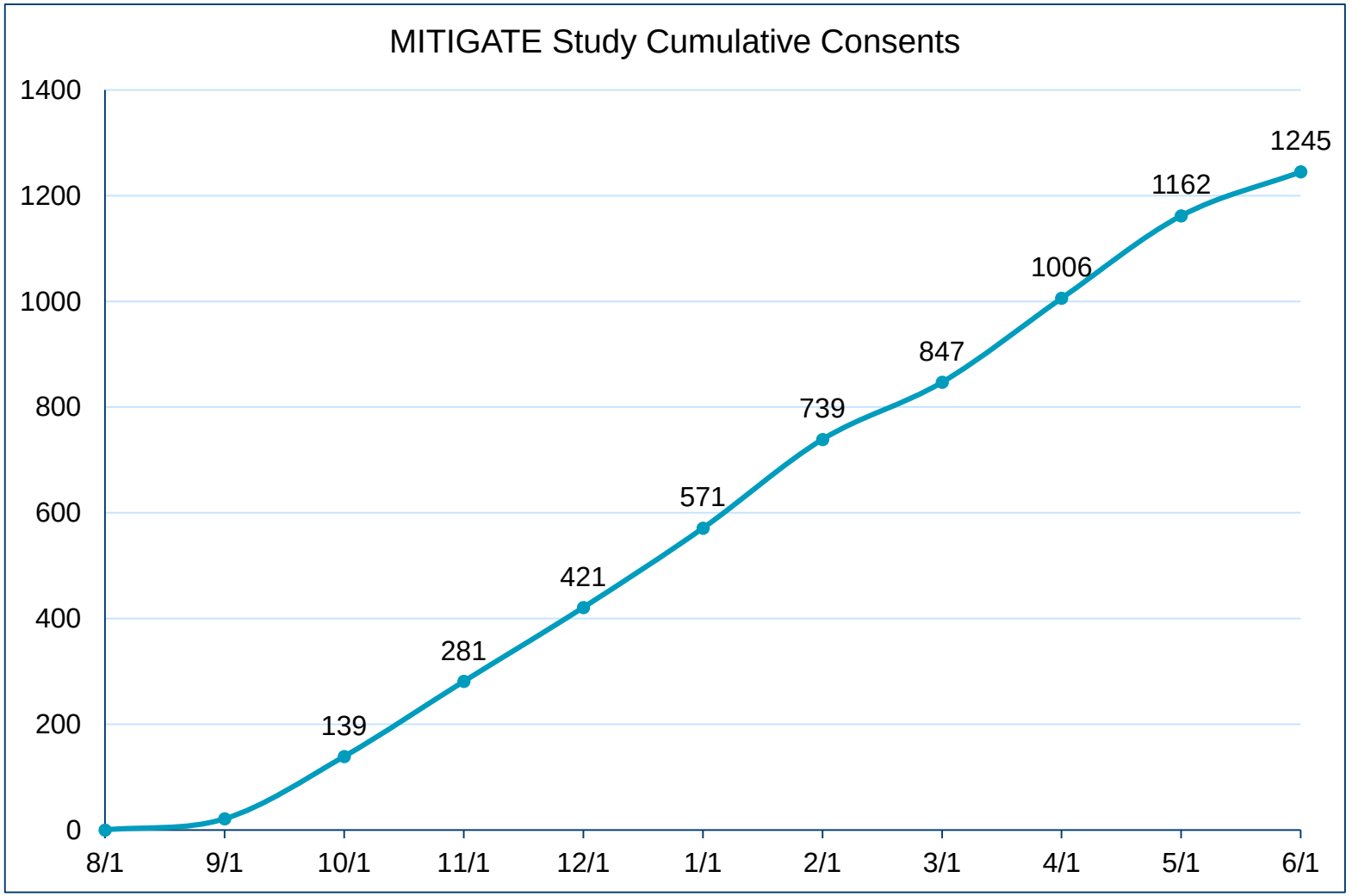
Recruitment



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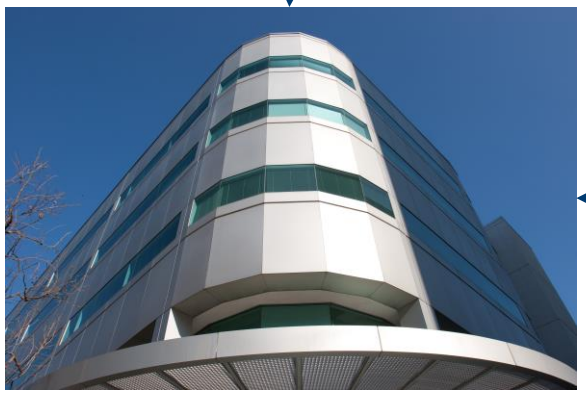
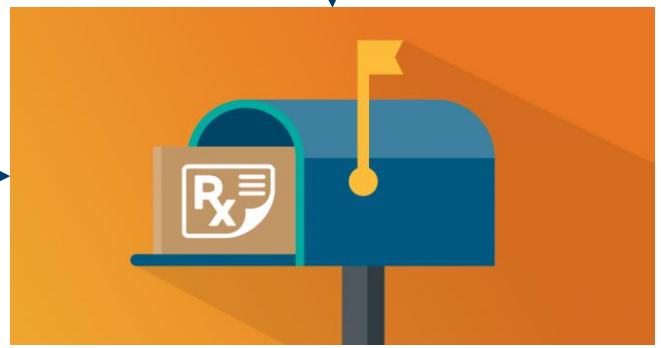
Setting

thrive





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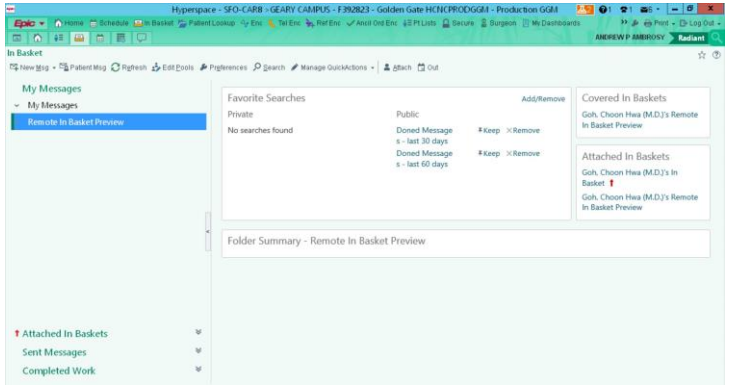
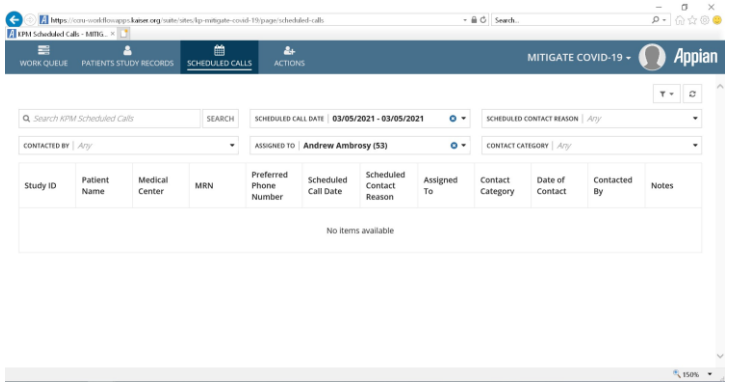
Organization and Tools

Electronic Health Record



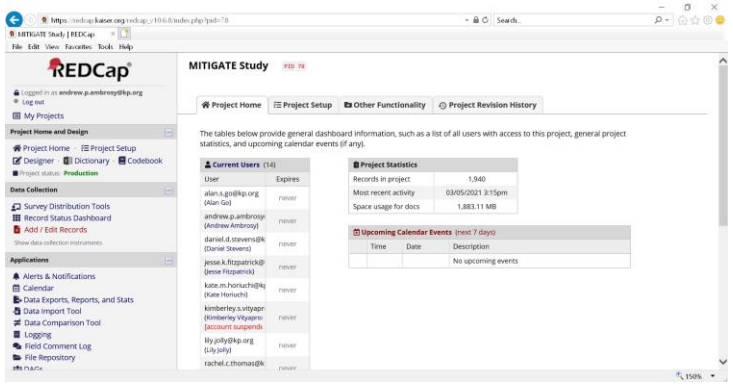
- Identify Eligible Patients
- Extract Baseline Data
- Send MD Staff Messages
- Follow-up for Outcomes

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

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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

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Flexibility – Adherence

Follow-up and Adherence	Intervention
Medication not started, N (%)	26 (**2%**)
Medication discontinued, N (%)	94 (**8%**)
Due to patient preference	69 (73%)
Due to adverse event	25 (27%)
Reached minimum follow-up, N (%)	17 (1%)
Withdrawn from study, N (%)	4 (**0.3%**)
Days on IPE	
Mean (SD)	116 (81)
Median (IQR)	115 (45.5 to 183)
Range	0 – 287

Abbreviations: N = number, IPE = icosapent ethyl; SD = standard deviation; IQR = interquartile range

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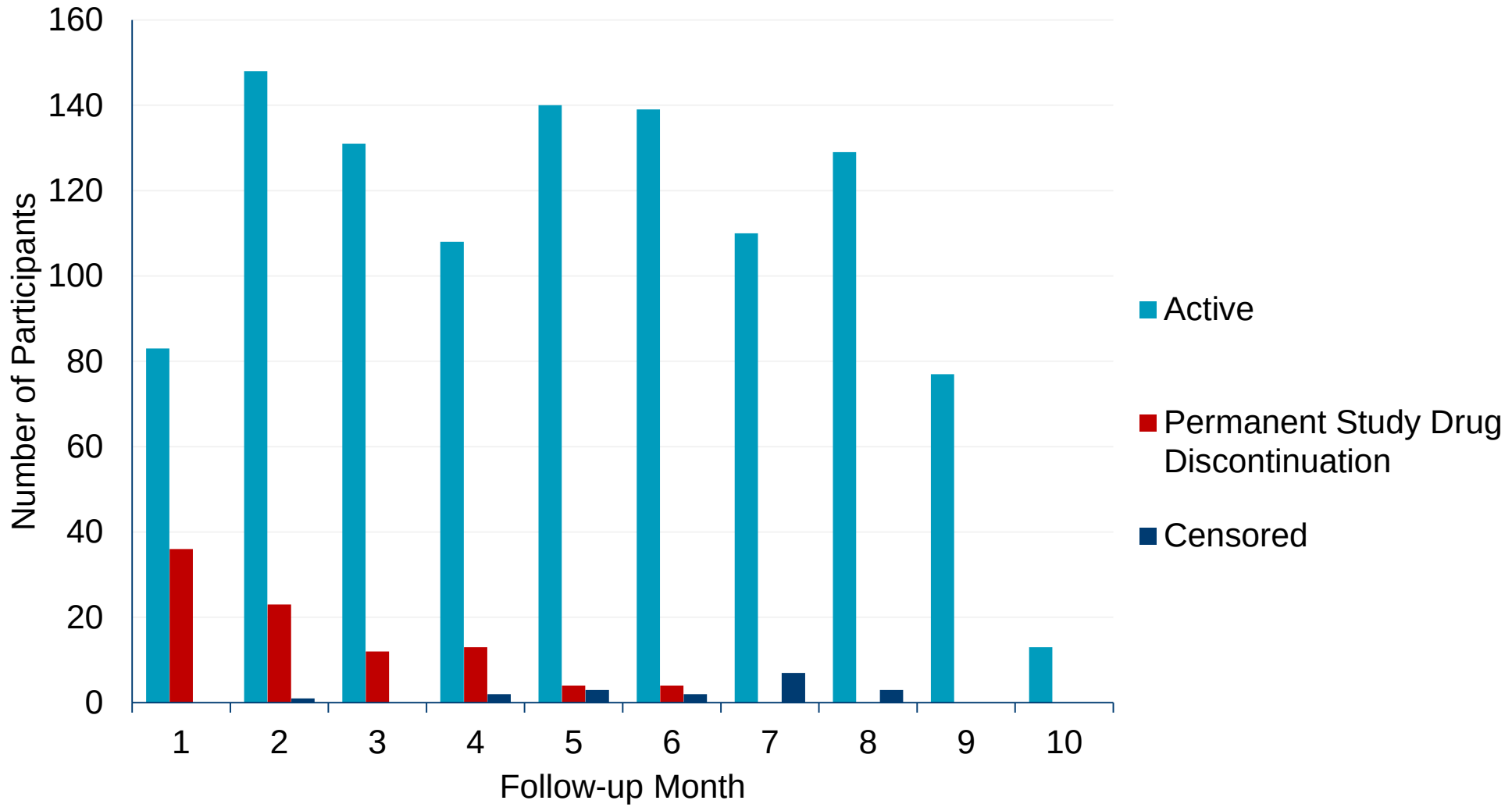
Flexibility – Adherence (Continued)



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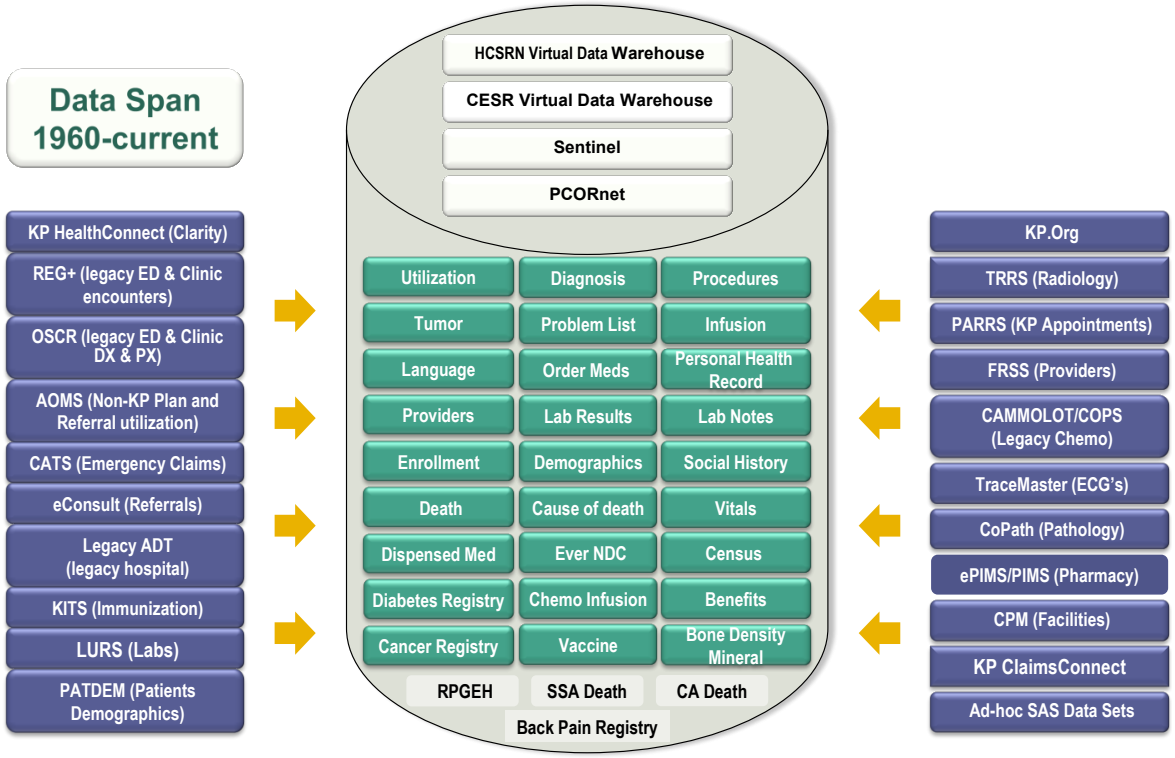
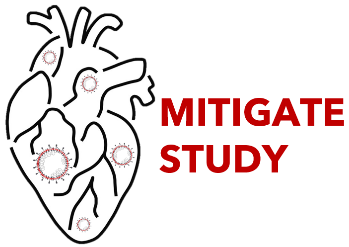
Follow-up

- 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





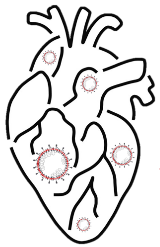
Co-Primary Outcomes

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

Endpoint	Overall
Moderate-to-severe confirmed viral URIs	1.0 per 100 PY
Encounters without low SpO_2/supplemental O_2 requirement	1.4 per 100 PY
Positive lab tests only	3.9 per 100 PY

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

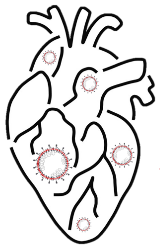
Note: To date, all viral URIs detected have been COVID-19 and appear robust based on blinded quality checks



Co-Primary Outcomes (Continued)

Endpoint	Overall
Worst clinical status at any point in time:	
1: Death	0.02%
2: Mechanically ventilated/extracorporeal membrane oxygenation	0.03%
3: High flow supplemental O_2	0.05%
4: Low flow supplemental O_2	0.15%
5: Hospitalized with no supplemental O_2	0.06%
6: Urgent Care or ED visit not leading to hospitalization	0.15%
7: No relevant clinical encounters	99.54%

Abbreviations: ED = emergency department



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Exploratory Outcomes

Exploratory Endpoints	Overall
All-cause death	1.4 per 100 PY
MACE (3-point)	3.4 per 100 PY
Expanded MACE (5-point)	4.9 per 100 PY
Hospitalizations for worsening heart failure	2.2 per 100 PY
All-cause hospitalizations and ED visits	71.2 per 100 PY

Abbreviations: MACE = major adverse cardiovascular events; ED = emergency department; PY = person years

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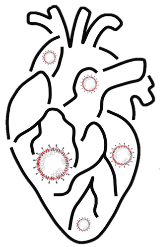
Safety Outcomes

Safety Endpoints	Overall
Incident atrial fibrillation/flutter	1.5 per 100 PY
Hospitalization for atrial fibrillation/flutter	0.4 per 100 PY
Hospitalized bleeding event	1.1 per 100 PY

Abbreviations: PY = person years



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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**

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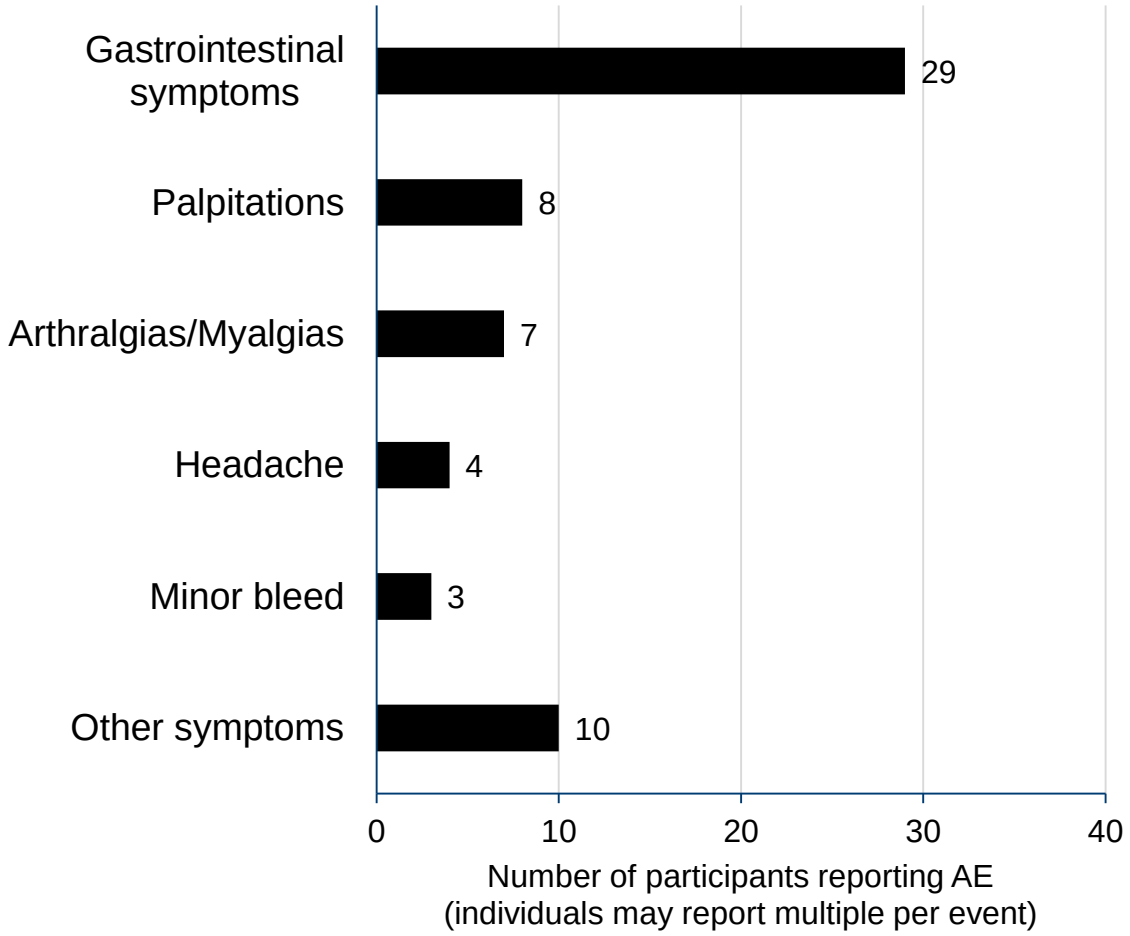
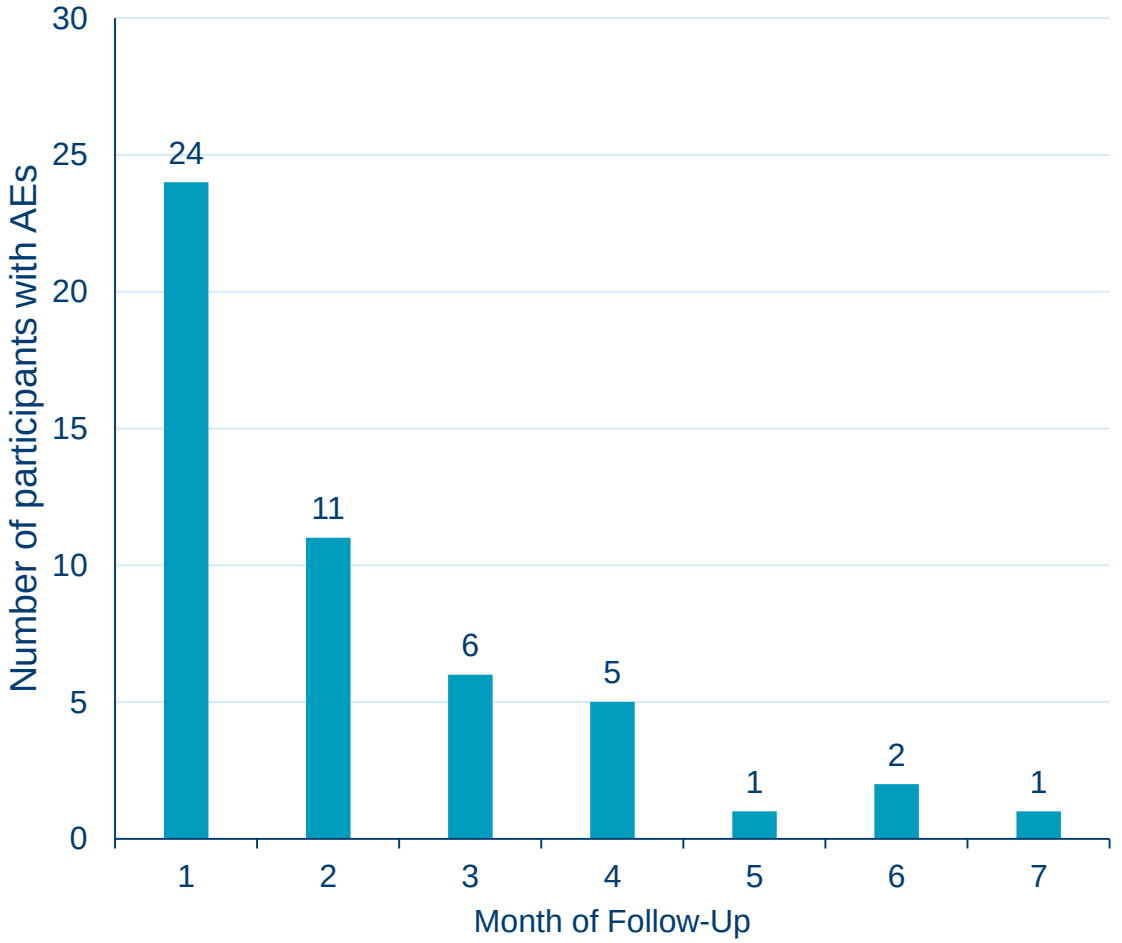
AEs/SAEs Leading to Discontinuation





~2% of study participations experienced an AE/SAE leading to permanent discontinuation

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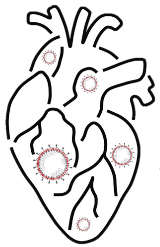

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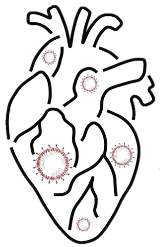
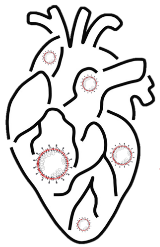
Statistical Analysis Plan

- **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



Statistical Analysis Plan (Continued)

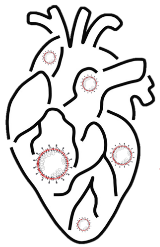
- MITIGATE adequately powered to detect a clinically meaningful difference between groups for actual event rates ≥10 events per 100 person-years
- Statistical assumptions **change** during a pandemic…



MITIGATE STUDY

Limitations

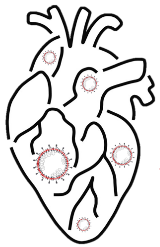
- Pre-randomization requires a high consent rate and may bias the results towards the null hypothesis
- Open-label nature has the potential to introduce bias, though outcomes are objective and assessment is blinded



MITIGATE STUDY

Limitations

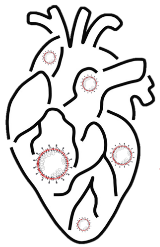
- No face-to-face clinical encounters, but patients receive monthly contact and refills are centrally managed
- Findings are not necessarily generalizable to prevention in other at-risk groups nor the use of IPE as an active treatment for symptomatic COVID-19



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



MITIGATE STUDY

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

MITIGATE STUDY

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QUESTIONS?