NIH:

RECOVER IVIG/Ivabradine in Long COVID + POTS

# A platform Protocol for Evaluation of Interventions for Autonomic Dysfunction in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)


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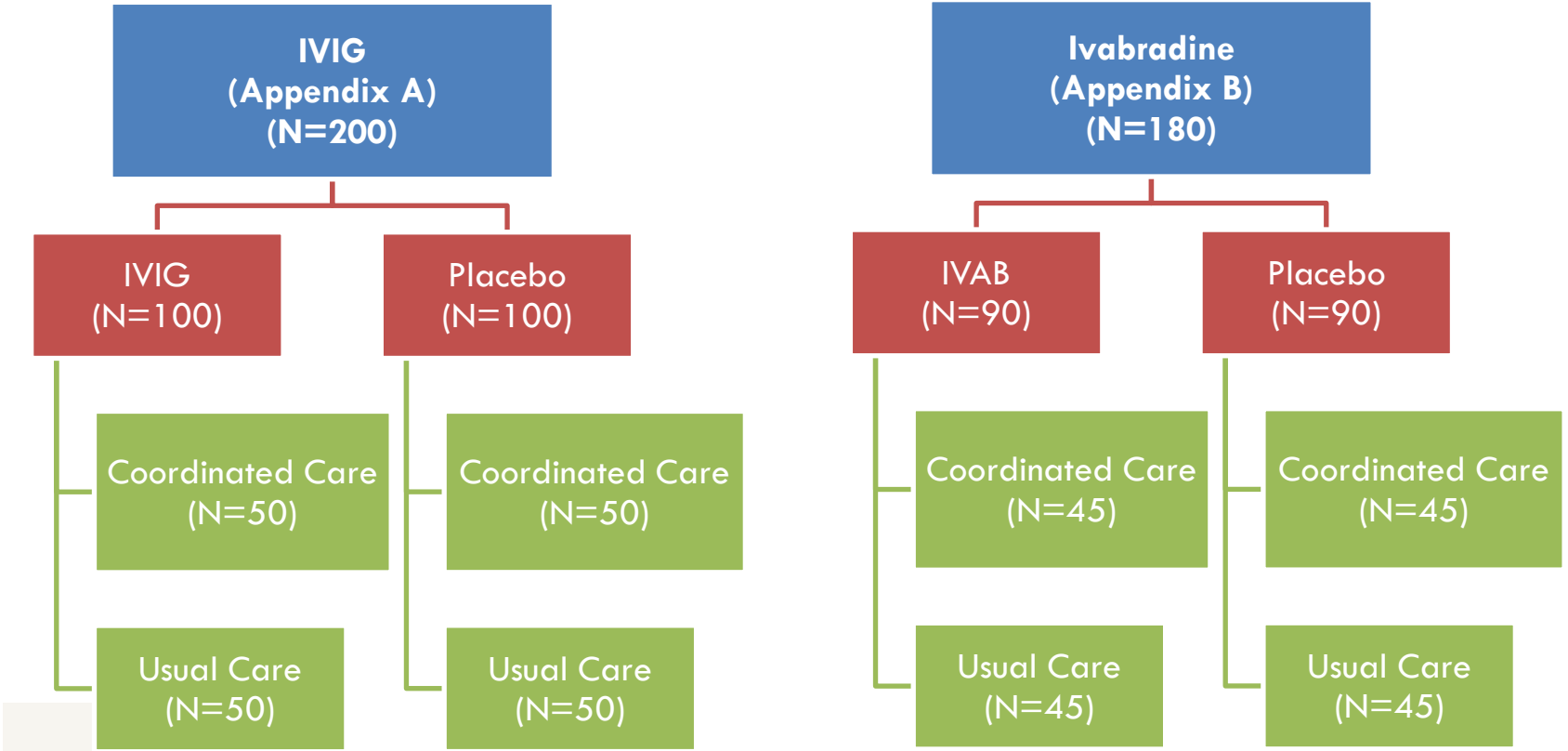
# RECOVER- Autonomic trial is designed to improve symptoms and functional ability in patients with Long COVID and POTS

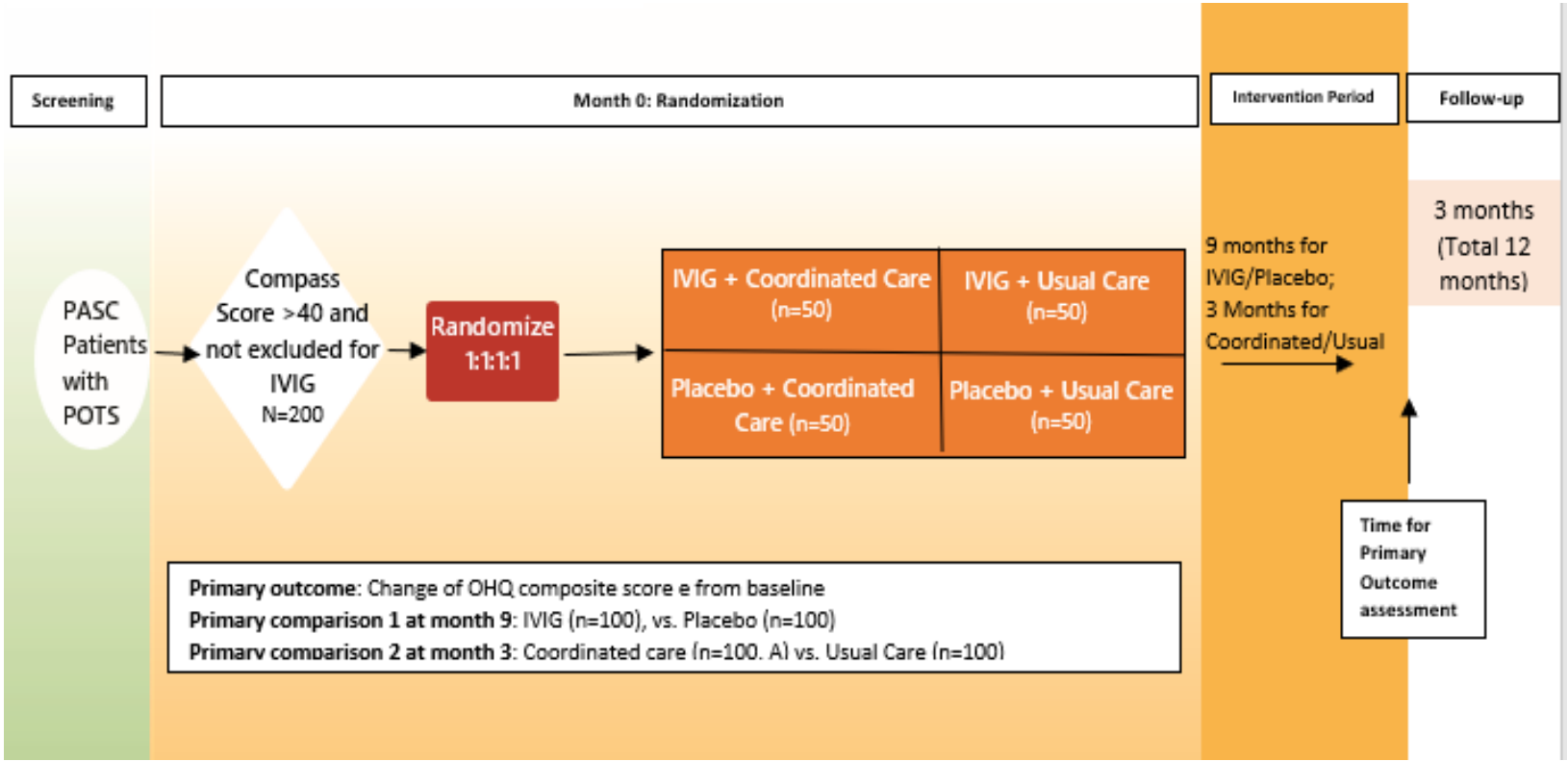
Three hypotheses being addressed:

1. IVIG (vs placebo) will improve symptoms and QOL at 9 months
2. Ivabradine (vs placebo) will improve symptoms and QOL at 3 months
3. Coordinated (Intensive) non-pharmacologic therapy and rehab with a care coordinator (vs usual care) will improve symptoms and QOL at 3 months

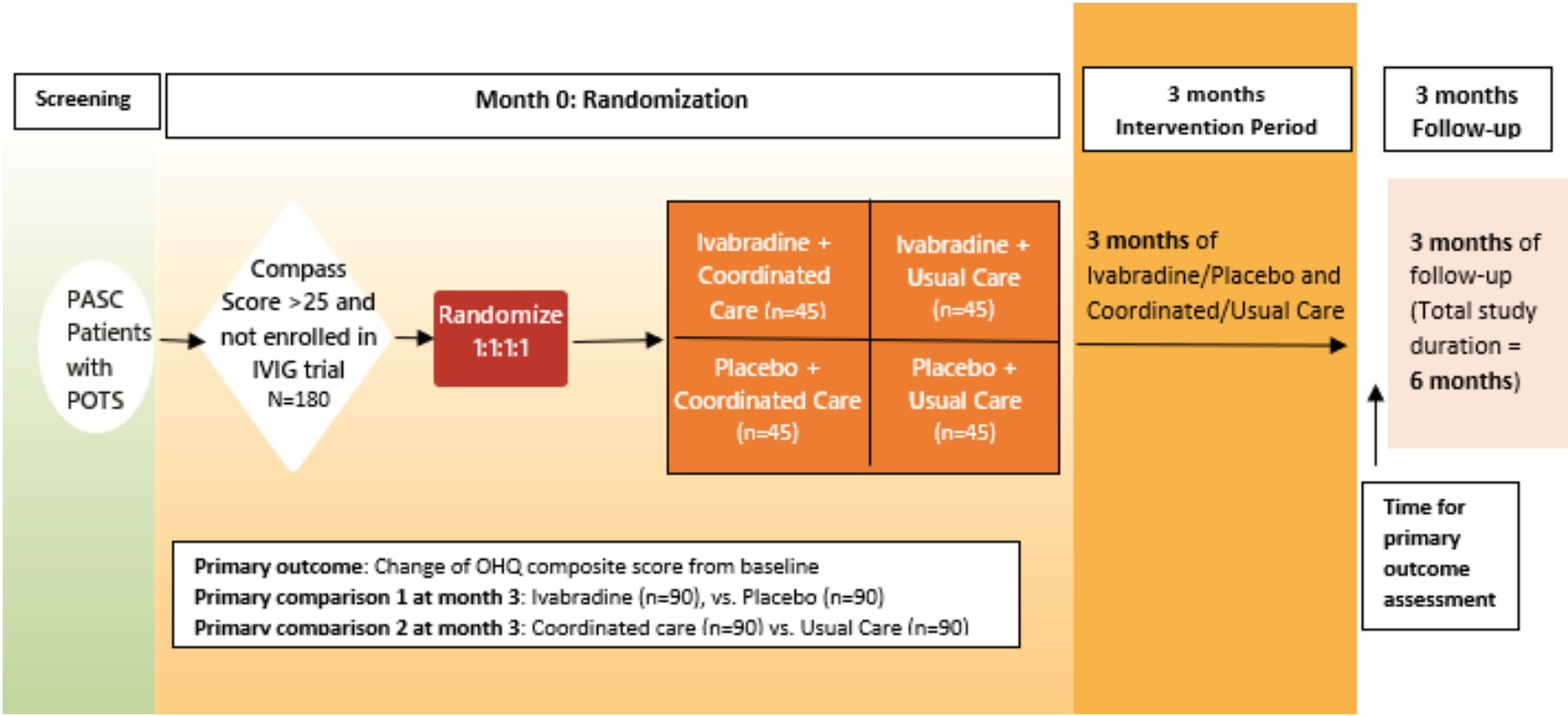
# Overview of **Drug** and **Non-pharmacological Interventions**



# Study Design, IVIG arm



# Study Design, Ivabradine arm



# **Coordinated Non-drug Care:** Activities

1. **Salt:** Consume 10 grams of salt each day (~1¾ teaspoons) using the provided measuring spoons
2. **Water/fluids:** Consume at least 2 liters (64 ounces) of water each day using the provided water bottle
3. **Abdominal compression:** Wear the provided compression belt around stomach while doing upright activities like shopping, cooking, walking, etc.
4. **Physical Activity:** Perform recommended exercises using the provided yoga mat and stretch bands. Exercises can be tailored to their preference, ability, and schedule
5. **Blood Pressure/Heart rate:** Check supine and standing BP/HR weekly (last day of the week) using the provided BP machine
6. **Weekly log:** Fill out weekly paper log (last day of the week) and enter data in Medidata eCOA (discussed in IM Session 2)
7. **Weekly check-in:** Discuss activities with care coordinator via phone or at in-person visits

# Study Activities

## IVIG Arm (12 Months)

- **Screening (remote)**
- **Baseline Visit**
- **Clinic Visits: Month 3, 6, & 9**
- **Follow-up Visit: Month 12**
- **Weekly Infusions**
- Informed Consent
- Medical Record Screening and Data Collection
- Blood, stool and nasal swab collection
- Patient Reported Outcomes (QOL of assessments)
- Safety Assessments
- Autonomic Function Testing (if available at site)
- **Skin Biopsy**
- Weekly Care Coordinator check in with participant (phone) (non-pharma coordinated care only)

## Ivabradine Arm (6 Months)

- **Screening (remote)**
- **Baseline Visit**
- **Clinic Visits: Month 1 & 3**
- **Follow-up Visit: Month 6**
- **Weekly check in (phone) with participant to monitor study drug compliance in month 1**
- Informed Consent
- Medical Record Screening and Data Collection
- Blood, stool and nasal swab collection
- Patient Reported Outcomes (QOL of assessments)
- Safety Assessments
- Autonomic Function Testing (if available at site)
- Weekly Care Coordinator check in with participant (phone) (non-pharma coordinated care only)

# Inclusion Criteria (protocol V0.1)

**Inclusion Criteria for Overall Enrollment**

- ≥ 18 to < 60 years of age at the time of enrollment
- Previous suspected, probable, or confirmed SARS-CoV-2 infection, as defined by the Pan American Health Organization
- Participant identifies moderate autonomic symptoms (defined as COMPASS >25 ) following a SARS-CoV-2 infection that has persisted for at least 12 weeks and is still present at the time of consent
- Abnormal active standing test defined as presence of orthostatic tachycardia (an increase of 30 bpm or more in heart rate within 10 minutes upon standing without orthostatic hypotension) and experiencing orthostatic symptoms
- **Additional Inclusion Criteria for Ivabradine**
- COMPASS-31 Score > 25 and not enrolled in the IVIG appendix

**Additional Inclusion criteria for IVIG**

- COMPASS-31 Score > 40

# Platform Protocol Overview (protocol V0.1)

| | |
|---|---|
| **Design** | Randomized Factorial Clinical Trial, Platform Protocol |
| **Regulatory Status/ Phase** | Phase 2 |
| **Patient Population (#)** | 180-200 for each study |
| **Description of Sites** | Up to 75 sites in the US<br><br>Participants will be recruited from various acute COVID-19 trials and existing RECOVER initiatives including, but not limited to, the longitudinal cohort, the RECOVER Registry, as well as other sites and research communities. |

# Study Objectives (protocol V0.1)

| OBJECTIVES | OUTCOME MEASURES | ENDPOINTS |
|---|---|---|
| **Primary** | | |
| Evaluate the effect of study intervention versus control on orthostatic intolerance outcome measures | Orthostatic Hypotension Questionnaire (OHQ) | Change from baseline to end of intervention (EOI) |
| **Secondary** | | |
| Evaluate the effect of study intervention versus control on symptom-specific outcome measures | Composite Autonomic Symptoms Score 31 (COMPASS-31)<br><br>POTS Symptom Score | Change from baseline to EOI |
| Describe the effect of study intervention versus control on performance-based and vital sign outcome measures | Active Stand Test and Vanderbilt Orthostatic Symptoms Score (VOSS)<br><br>Ambulatory blood pressure (BP) and heart rate (HR) measurements<br><br>6-min Walk Test | Change from baseline to EOI |

| OBJECTIVES | OUTCOME MEASURES | ENDPOINTS |
|---|---|---|
| **Secondary** | | |
| Evaluate the effect of study intervention versus control on symptom burden and quality of life | PROMIS-29 + 2 Questionnaire<br><br>PASC Symptom Questionnaire | Change from baseline to EOI |
| Compare the effect of study intervention versus control on specific tracked measurements | Wearable device measuring accelerometry (step count, sleep, HR) | Change from baseline to EOI |
| Evaluate the effect of study intervention versus control on autonomic function tests | Autonomic function test at specialized sites:<br>• Head up tilt (HUT) test<br>• Valsalva maneuver with a pressure of 40 mmHg for 15 seconds<br>• Deep breathing test<br>• Skin biopsy (if available)<br>• Transcranial doppler (TCD), if available | Change from baseline to EOI |
| Characterize the safety and tolerability of study intervention for treatment of PASC | Serious adverse events (SAEs) and Events of Special Interest (ESIs) | Proportion of participants who experience individual SAEs and the proportion who experience any one or more SAEs<br><br>Incidence of SAEs leading to discontinuation will also be summarized<br><br>Events of Special Interest (ESIs) will be summarized |

| OBJECTIVES | OUTCOME MEASURES | ENDPOINTS |
|---|---|---|
| **Exploratory** | | |
| Evaluate the effect of study intervention versus control on relevant biomarkers and cognitive function | • Viral biomarkers<br>• Autonomic function biomarkers<br>• Immune biomarkers<br>• Inflammatory biomarkers<br>• Endothelial function biomarkers<br>• Cognitive function (CCL11) | Change in biomarker(s) from baseline to EOI |

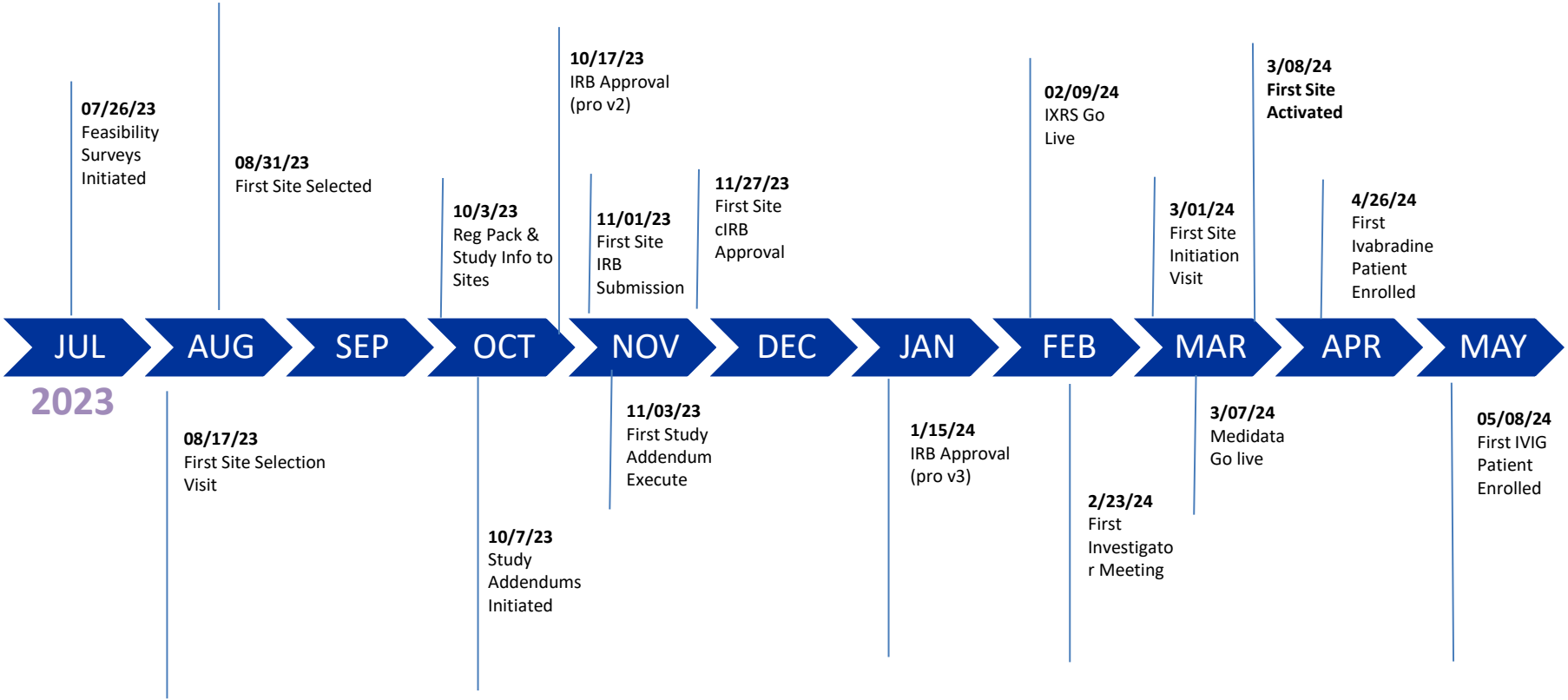
# Study Interventions

| Study Intervention | Dosing | Rationale |
|---|---|---|
| Active Treatment:<br>**IVIG**<br><br>Placebo:<br>Albumin | IVIG: 0.5 g/kg every week, for a total of 2 g/kg every month<br><br>Pre- and Post-Dose for IVIG and placebo:<br>Fluids: 0.9% NaCl 500 mL IV<br>• Acetaminophen 650 mg and Claritin 10 mg (given 30 min before IVIG and as needed after IVIG)<br><br>Note: Some patients may require strong pre-medication (steroids, Toradol) or additional fluids | IVIG is a mixture of immune globulins consisting primarily of IgG with trace amounts of IgA and IgM. IVIG has been used to treat several viral infections, and approximately 40-50% of POTS is thought to be immune-mediated. |
| Active Treatment:<br>**Ivabradine**<br><br>Placebo:<br>Placebo tablet | Ivabradine: starting dose will be 5 mg twice a day, and the dose will be modified if needed at the 1 month clinic visit.<br><br>• Resting HR 60-80 = 2.5 mg BID<br>• Resting HR >80 = 5 mg BID<br>• Max dose, 7.5 mg BID if resting HR >90 | Ivabradine has been used to treat symptoms such as tachycardia and POTS with improvement in a small randomized trial and in observational studies. |

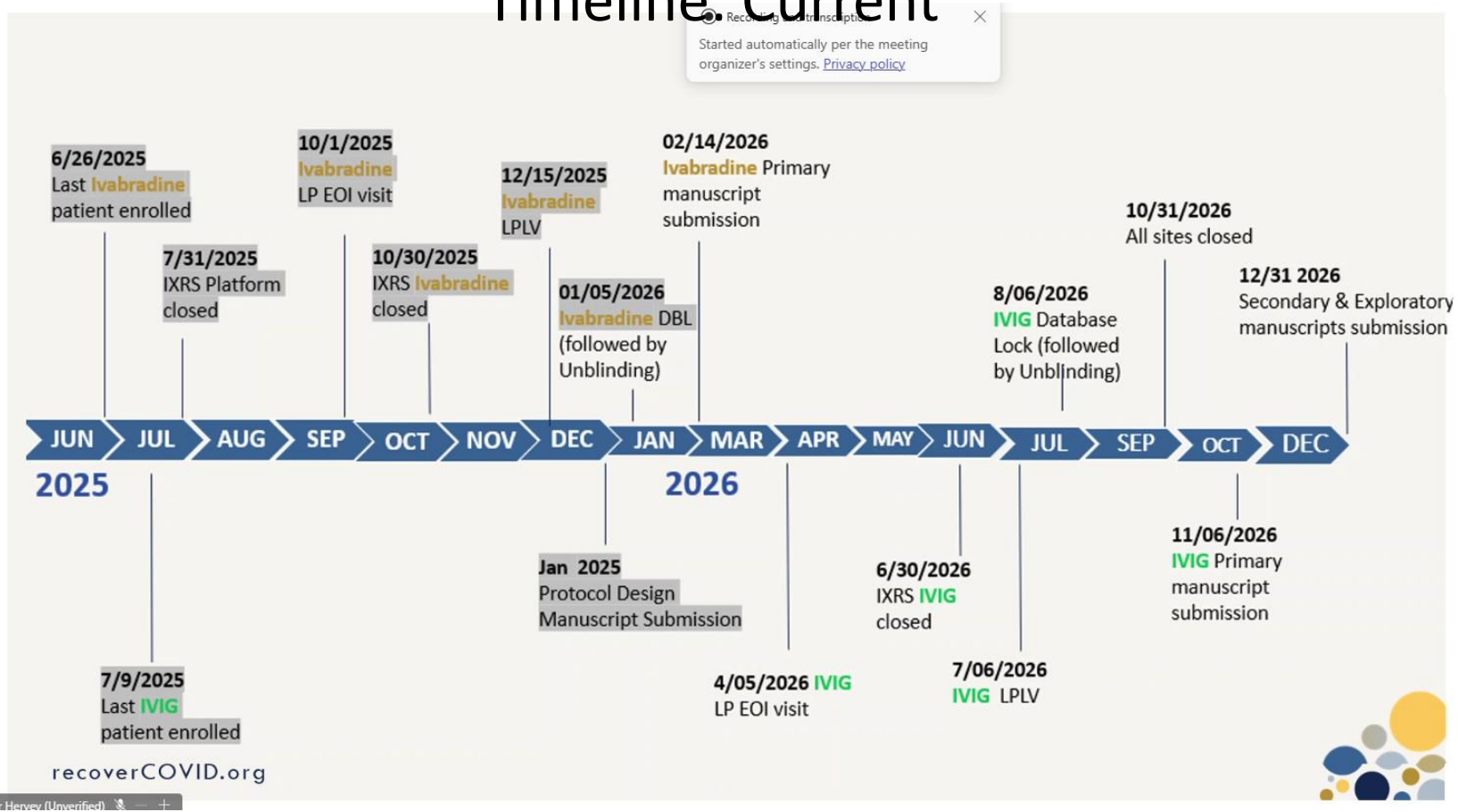
# Study Interventions – (Cont'd)

| Study Intervention | Dosing | Rationale |
|---|---|---|
| Intensive non-pharmacologic care | On a regular basis for 3 months, including care coordinator once a week<br><br>Volume expansion through high salt diet (6-9 grams of salt), abdominal binding, compression stockings, exercise/rehabilitation, nutrition counseling, motivation, education, and assisted care through care coordinator | Currently, the foundation of treatment for POTS, and for POTS in patients with PASC, is non-pharmacologic therapy. Achieving adherence in the general population is difficult. Therefore, having this incorporated into a controlled clinical trial will provide the first reliable evidence as to the role of these non-pharmacologic practices in patient care. |

# Timeline: HISTORICAL



# Timeline: Current



# Ivabradine Appendix Updates

- Number of sites activated for Ivabradine: 48
- Number of sites enrolled participant(s): 40
- Total number of participants enrolled: 181
- First Patient enrolled: 4/26/24
- Last Patient Last Visit: 12/15/25
- Database lock: 1/5/26

# Thank you !