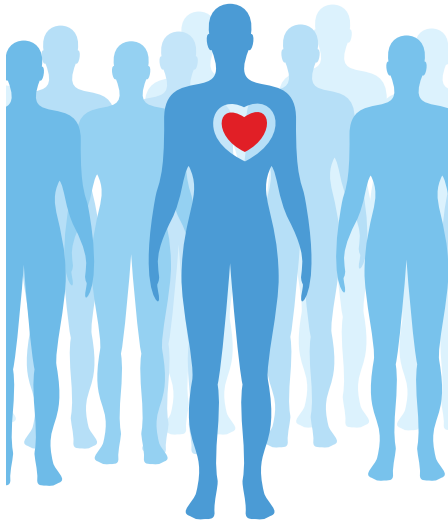


PROJECT UPDATE: A YEAR IN REVIEW



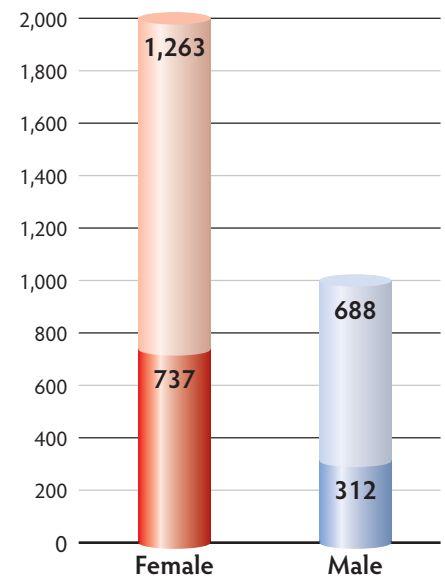
There is so much we hope to learn about how each piece of the puzzle fits together.

The VIRGO project enrolled its first participant in August 2008, and with the help of more than 97 hospitals across the United States, over 1049 young women and men have agreed to participate in VIRGO and share their stories.

In addition to the high overall participant enrollment in VIRGO, the hard work and commitment of physician investigators and site coordinators alike have led to an exceptional genetic consent rate. To date, 95% of participants have agreed to provide a small blood sample for genetic analysis.

Regardless of gender, VIRGO participants across the country represent a diverse population. Some have no history of cardiovascular disease, appear healthy and maintain a regular exercise schedule, while others smoke, have diabetes or high blood pressure among other risk factors. There is so much we hope to learn through the participants' stories and how each piece of the puzzle fits together, both in terms of risk factors for heart attacks as well as recovery trajectories and outcomes.

VIRGO Enrollment
(11/2009)



Currently approximately 3% of those enrolled in VIRGO have chosen to discontinue participation in the project. Among the most frequently cited reasons for discontinuing participation is because "there is just too much going on in [their] life."

It is important for us to continue to identify these reasons and encourage ongoing participation.

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Working through Challenges

The Yale team continues to work with site coordinators to ensure adequate minority representation and diversity among VIRGO participants.

Enrollment of women in VIRGO is going well and we are close to meeting our enrollment target. While we've met the overall target for women, when taking into account the distribution of minority groups enrolled, we're just 14% short of our annual enrollment target for African American women.

In contrast however, the enrollment of men and minorities in VIRGO across the country has been lower than anticipated. As a result the Yale coordination team continues to work closely with site coordinators in an effort to tackle site specific challenges, and ensure all eligible participants are screened and approached for consent and enrollment. In VIRGO, White men are just 13% short of the annual enrollment target, while Hispanic men follow close behind, 16% short of the annual target. Enrollment of eligible African American men however is 74% short of the annual enrollment target. Greater effort and coordination is needed to support the consent and enrollment of young men, particularly of young Black and Hispanic descent.

The Yale team continues to work with site coordinators, particularly at hospitals serving notably large minority populations, in an effort to ensure adequate minority representation and diversity among VIRGO participants. To support this effort, recent brownbag series have focused on the enrollment of male and minority participants. Leading the presentations, Dr Gail D'Onofrio, Chief of Emergency Medicine at Yale University and Dr Erica Spatz, a Yale Robert Wood Johnson Clinical Scholar have endeavored to provide helpful guidance on enrolling male and minority participants. These presentations among others in the brownbag series are available on the VIRGO study website (www.virgosite.org).

We will continue to identify opportunities to support successful enrollment, and encourage sites to share their stories with us so that we can learn from these experiences and meet our enrollment targets.

Taking the Time to Talk Recovery

Learning how participants fair over time after seeking care and receiving treatment is an important aspect of VIRGO. The Yale Follow-up Center is hard at work completing the 1 month and 12 month participant interviews. These interviews will allow us to characterize participants and their recovery since their admission to your hospital. We're excited to share that the Follow-up Center has successfully completed 94% of the 1 month interviews for participants who have entered their 1 month window.

As you might have guessed, keeping up with participants can be quite a challenge. Changes in their lives can often translate to financial difficulties or changes in lifestyle such as living

arrangements or return to work. And once again, the team here at Yale is so thankful for the teamwork exhibited by site coordinators like you who stepped up and were instrumental in helping us get in touch with some of these hard-to-find participants and complete their follow-up interviews.

94%
of the participant
1 month interviews have
been completed.

The Follow-up Center has just begun the 12 month interviews for our earliest enrolled participants, so stay tuned for our exciting updates in the coming

months. Just as you've faithfully identified and enrolled eligible participants for this project, the team here at Yale is equally committed to completing every possible interview. This is a tremendous accomplishment we will work hard to maintain throughout the project. Obtaining blood is always a challenge in scientific studies.

Drawing on Teamwork

We weren't sure how successful we'd be obtaining blood samples from participants one month after their admission for a heart attack. It does take a collective effort from the entire VIRGO team. Over the past year, Yale

and site coordinators have worked hand in hand to orchestrate the collection of blood samples, and have maintained a high blood collection rate of 81%.

Working Hand in Hand

Some participants earn their living on the national highways and byways hauling goods across the country. As the VIRGO team learned over the past year, scheduling these participants for a blood draw can be quite a challenge.

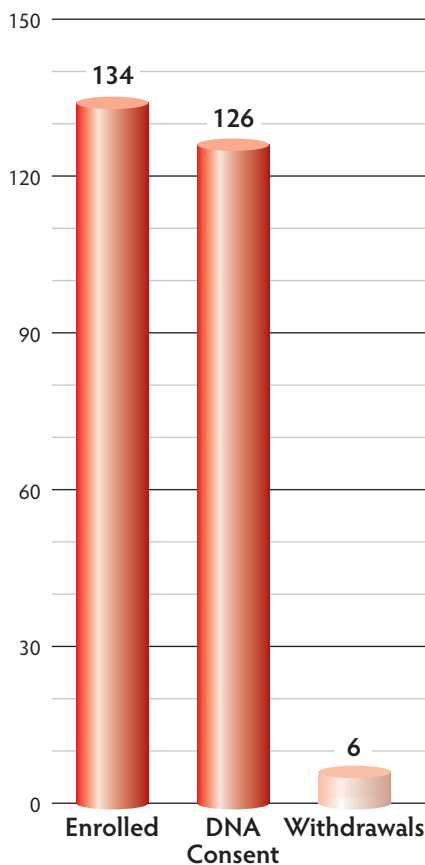
By working with site coordinators across the country, the VIRGO team has been able to successfully schedule appointments and collect blood samples at other participating sites.

The Yale team extends its deepest gratitude to the site coordinators who played a role in orchestrating these timely blood draws. Please contact the Yale Coordinating Center if you need assistance coordinating blood draws at other participating sites.

IM-JOVEN

Spain

IM-JOVEN Enrollment
(11/2009)



In the summer of 2008 Dr. Hector Bueno, the primary investigator for Infarto en la Mujer Joven (IM-JOVEN), came with his family to spend 6 months at Yale University, where he contributed to the development of the VIRGO protocol and IM-JOVEN's alignment with VIRGO. IM-JOVEN is a sister study in Spain led by an alliance of local Spanish partners, and presents an opportunity at Yale to compare data with similarly aged young women and men diagnosed with heart attacks in Spain.

Following Dr Bueno's departure from Yale at the end of 2008, IM-JOVEN soon took shape, enrolling the first Spanish participant in March of this year. The Spanish team has been hard at work, and enrolled their 100th participant in early October. Among their more than 20 participating hospitals across Spain, *Universitari de Bellvitge* and *Vall d'Hebron University* both hospitals in Barcelona, and *Virgen de la Victoria* hospital in Malaga have taken the lead, each enrolling more than 10% of IM-JOVEN's participants.

Hospitals in Spain participating in IM-JOVEN collaborate closely with notable partners such as ANAGRAM a clinical research organization

responsible for the study-wide coordination as well as participant data collection and entry, Echevarne laboratories attends to the timely processing and storage of participant blood samples, while Projectam conducts post-discharge participant interviews by telephone.

IM-JOVEN has been made possible through the generous financial support from *Fondo de Investigaciones Sanitarias del Instituto Carlos III* (Spanish Ministry of Science and Technology), and *Centro Nacional de Investigación Cardiovascular* (CNIC), and in partnership with the Working Group on Ischemic Heart Disease of the Spanish Society of Cardiology, and the Spanish cardiovascular research networks RECAVA and HERACLES.

Together with the data obtained by the IM-JOVEN team, we hope to better understand the influence of healthcare systems on the outcomes for young patients in distinctly different populations diagnosed with acute myocardial infarctions.

Australia

VIRGO has extended its influence to 'the Land Down Under' with the Queen Elizabeth Hospital in Adelaide recruiting the first VIRGO-Australia patient in the Southern Hemisphere. Adelaide has a population of one million and is renowned for its fine wines. The VIRGO project has now been inducted at two of the city's major teaching hospitals with plans to include more. Although recruitment only began 5 weeks ago the 'Aussies' have already recruited 7 patients and are enthusiastic about their involvement.

The Principal Investigator, John Beltrame, is a cardiologist with a strong research interest in coronary artery spasm and microvascular dysfunction. His research has defined racial differences in vasomotor reactivity (between Japanese and Caucasians), identified a new coronary microvascular disorder – the coronary slow flow phenomenon, and more recently characterized the frequency of angina amongst Australian stable angina patients.

John is well supported by the study coordinator, **Rachel Dreyer** (pictured), who is undertaking her doctoral studies in gender differences amongst patients with cardiovascular disease. She can often be seen working in the hospital at 7am, on a conference call with our resident Australian Yale Coordinator here in New Haven – Gabrielle Douglas. Her enthusiasm for the project has been 'infectious' and reflected in the rapid recruitment rate.

The VIRGO-Australia study is an independent project working in close collaboration with the VIRGO study, adopting the same study protocol and an Australian version of the case report forms. The Australian data will not only contribute to the major study endpoints but will also allow comparisons between cultures with different health care systems. Furthermore, using the local expertise in microvascular dysfunction, the Australian investigators will endeavor to explore mechanisms that may be contributing to gender differences.

The Australian data will allow comparisons between cultures with different health care systems.





Case Highlight

A 47 year old woman presents to the emergency department with a primary complaint of prolonged neck pain and prolonged left arm weakness, with worsened symptoms under exertion. The patient's EKG was abnormal with ST elevations (STEMI) and symptoms worsened upon admission, and relieved with nitroglycerine. The patient was admitted and sent to the catheterization lab, with a diagnosis of an acute anterior myocardial infarction with 85-90% stenosis in the left anterior descending coronary artery. Throughout the patient's admission however, the patient's troponin never rose above the upper reference limit of normal.

While the patient met both the inclusion criteria for age and evidence of ischemia, the patient was excluded from VIRGO in the absence of elevated troponins. The patient is believed to have an aborted myocardial infarction.

Protocol Clarification

A patient is eligible for inclusion if they present to the enrolling hospital's Emergency Department (ED) or they are transferred to the enrolling institution within 24 hours of the acute cardiac event. The primary reason for hospitalization must be due to a cardiac etiology with symptoms of ischemia, ECG changes or other evidence of myocardial necrosis. The patient must have elevated cardiac markers within 24 hours of presentation (with the only exception detailed below). The patient must be diagnosed with an Acute Myocardial Infarction (AMI) or an Acute Coronary Syndrome (ACS) with positive biomarkers (which is synonymous with AMI).

In some cases the clinical team may work toward a diagnosis of AMI. Other diagnoses may be ruled out throughout the hospitalization before it is determined that the patient had an AMI. Coordinators may approach the patient at any time during hospitalization once the clinical team has determined the diagnosis was AMI on admission.

Included	Excluded
Participants with AMI symptoms on presentation and abnormal cardiac markers in the first 24 hours.	Participants without abnormal cardiac markers (drawn but negative).
Participants diagnosed upon admission with an AMI but with no cardiac markers drawn. We have seen this occasionally with a patient taken directly to the catheterization laboratory and having what appears to be an active lesion dilated.	Participants that meet inclusion criteria but their diagnosis is something other than AMI or ACS.
	Patients who develop the AMI more than 24 hours after admission.

Team Recognition

The hard work and commitment of research teams across the country in support of VIRGO is truly humbling and deserving of recognition. Nevertheless, there are a few who have exhibited impeccable attention to detail completing the electronic case report forms and when forwarding patient records in the shortest time. To that end, would like to personally thank the teams at: 019 Central Maine Medical Center, 037 Parkview Hospitals, 090 Memorial Medical Center, 125 Pepin Heart Research Institute, 179 St John's Mercy Medical Research Institute, and 186 Genesis Medical Center for their noteworthy efforts.

Congratulations

Becky Toler, RN, BSN Clinical Research Nurse at Cardiovascular Research Foundation of Louisiana on the birth of her healthy 7 lbs 13 oz bouncing baby boy.

Dieuwke "Juka" Zolas, RN, Case Manager has amassed 30 years of nursing experience in intensive and cardiac care around the United States. Juka recently departed the clinical research team at Central Maine Medical Center to revive the congestive heart failure management program at the Center, aimed at transitioning patients from inpatient to outpatient care. Juka has been an invaluable partner in VIRGO, but leaves its coordination in the aptly able hands of Vyrl Romanella, LPN, BS Clinical Research Coordinator.

Joyce McGinty, MS, RN on her recent appointment as Director of Heart and Vascular Services at Sharp Grossmont Hospital. Joyce's commitment to cardiac critical care has spanned two decades, contributing to excellence of cardiac care at Sharp Grossmont Hospital.

Wendy Hori, RN in her future endeavors as the Nurse Manager of the Clinical Research Center at the Joslin Diabetes Center in Boston, Massachusetts.

Lauren McCune, RN on her recent promotion to Clinical Advancement Liaison at Butler Memorial Hospital.

We'd love to hear about your experiences and achievements, so don't be shy about sharing them your Yale Coordinator!

Regulatory Reminders

- Please ensure that Repository (DNA) Consent Form checkboxes are checked. This checkbox indicates if a participant wishes to provide a sample to the VIRGO databank. If checkboxes are left blank, the VIRGO Coordinating Center will ask participating sites to send incomplete Repository Consent Forms to participants so that they can indicate their choice on the consent form.
- Remember to submit a copy of all documentation to the VIRGO Coordinating Center, including annual continuing review letters and newly stamped consent forms.
- Remember to submit any consent form or protocol modifications to the VIRGO Regulatory Specialist prior to submission to your IRB.
- Please also submit site specific approvals, including personnel additions and removals.

Thank you for your support. Contact the VIRGO Regulatory Specialist if you have any questions or require assistance with regulatory activities:

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 Regulatory Specialist and
 Study Coordinator
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Variation In Recovery: Role of Gender on Outcomes of Young AMI Patients

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Daoud Mikhail, MIA
Monique Plinck



Yale University School of Medicine

Congratulations 1000th Participant

Senatra Hospitals of Virginia enrolled the VIRGO's 1000th participant on November 3, 2009. Thank you to each and every site coordinator for their hand in achieving this notable milestone.

Mark Your Calendar Wear Red Day

Circle February 5, 2010 on your calendars to join hands with the American Heart Association (AHA) across the country in the fight against heart disease in women on Wear Red Day! To learn more about the national cause to increase awareness and help women reduce their risk of heart disease please visit GoRedForWomen.org. We'll share some creative ideas and material to mark GoRedForWomen on the VIRGO website (www.virgostudy.org), but also love to hear learn how you and your hospital is planning for mark Wear Red Day. We also invite you to share your plans, ideas and photos with us.



A frequent request from sites has been for greater communication and information sharing across our partner sites. In response to this feedback, we've created a VIRGO forum on the Cardiovascular Outcomes (CVO) website with one-stop-shopping in mind—providing project information, updates, real-time communication among sites, access to study documents and related publications, a calendar of events and more.

For access to study material, be sure to join the VIRGO group by registering at <http://cvoutcomes.org/signup>.