Randomized comparison of the clinical

Outcome of single versus

Multiple

Arterial grafts

Weill Cornell Medicine

July 2019

Dear Valued ROMA Study Community,

Thanks to your contributions, ROMA Study is on target for recruitment! We expected 1118 enrollments in June 2019 . We reached **100%** of that goal before the months end.

Well Done!

Our team submitted a grant proposal to the National Institute of Health (NIH) for a Quality of Life sub-study (The ROMA:QOL study) in June. We thank Ruth Masterson Creber, PhD and all of your support for making it possible.

More information to come!

ROMA received recognition from the international community for filling "the gaps in evidence" in CABG methodology research. **See Page 17** for a clip from the **2018 ESC/EACTS Guidelines on myocardial revascularization[1].**

Cheers to the Innsbruck Medical University Team of Austria on randomizing the

1000th ROMA participant!

Top 5 Enrollers

1. Jilin Heart Hospital, China
2. Dedinje Cardiovascular Institute, Serbia
3. Innsbruck Medical University, Austria
4. Medical University of Vienna, Austria
5. European Hospital, Italy

Please keep reading for more updates and our featured ROMA site:

Fondazione Policiclinico Universitario "Agostino Gemelli": Rome, Italy

You each play a huge role towards accomplishing the goal of finally providing an answer to the 30-year old debate on the role of multi-arterial CABG. Thank you for your invaluable contribution.

As our subject population grows and we enter the long term follow up phase of the trial, we will begin shifting greater focus towards data quality and monitoring.

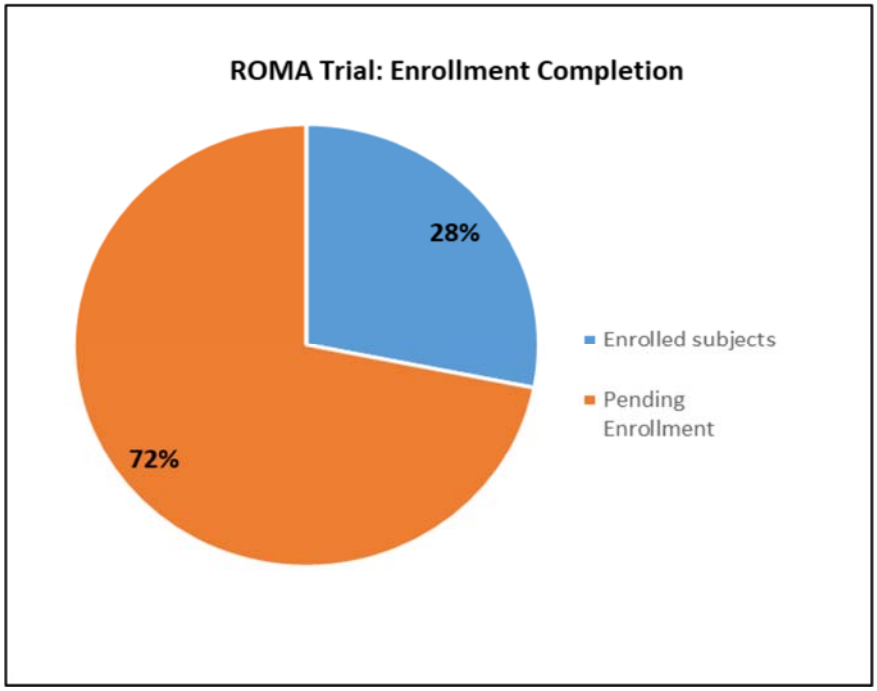
The following items are some of the areas we are focusing in on:

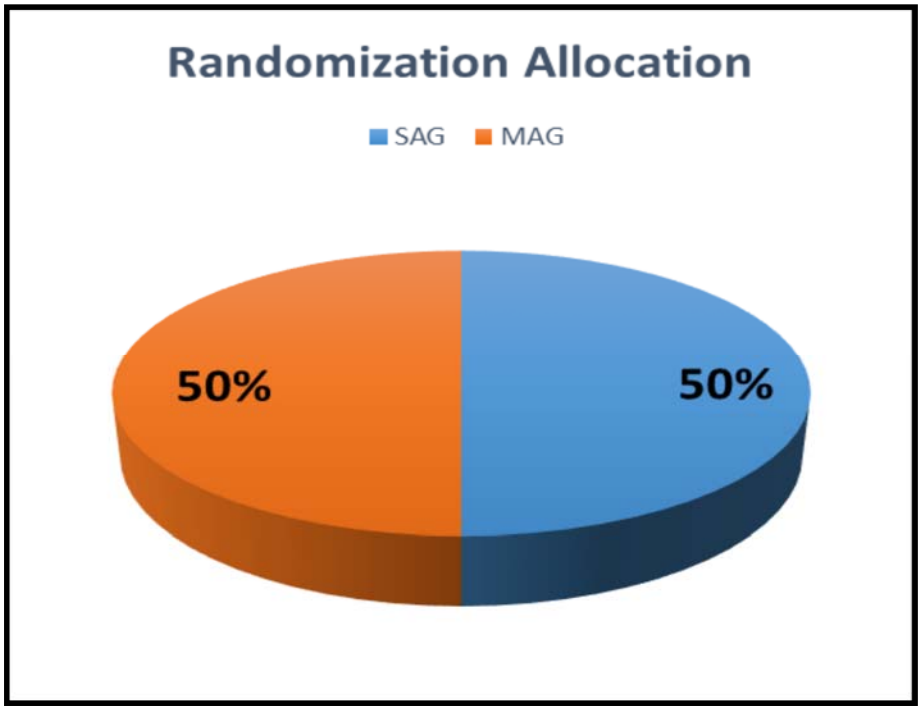
- **Page 7**: Reduction of long term loss to follow-up
- **Page 8: Case report forms** (CRFs) are being entered into the Clinvestigator database in a timely manner
- **Page 9:** Ensuring proper documentation of **adverse events** are uploaded on the ROMA database for centralized review and analysis
- **Page 10:** Ensuring **regulatory compliance** and Good Clinical Practice are being followed at each site
- **Page 11:** Standardizing methods of documenting **informed consent** and uploading to the Clinvestigator database

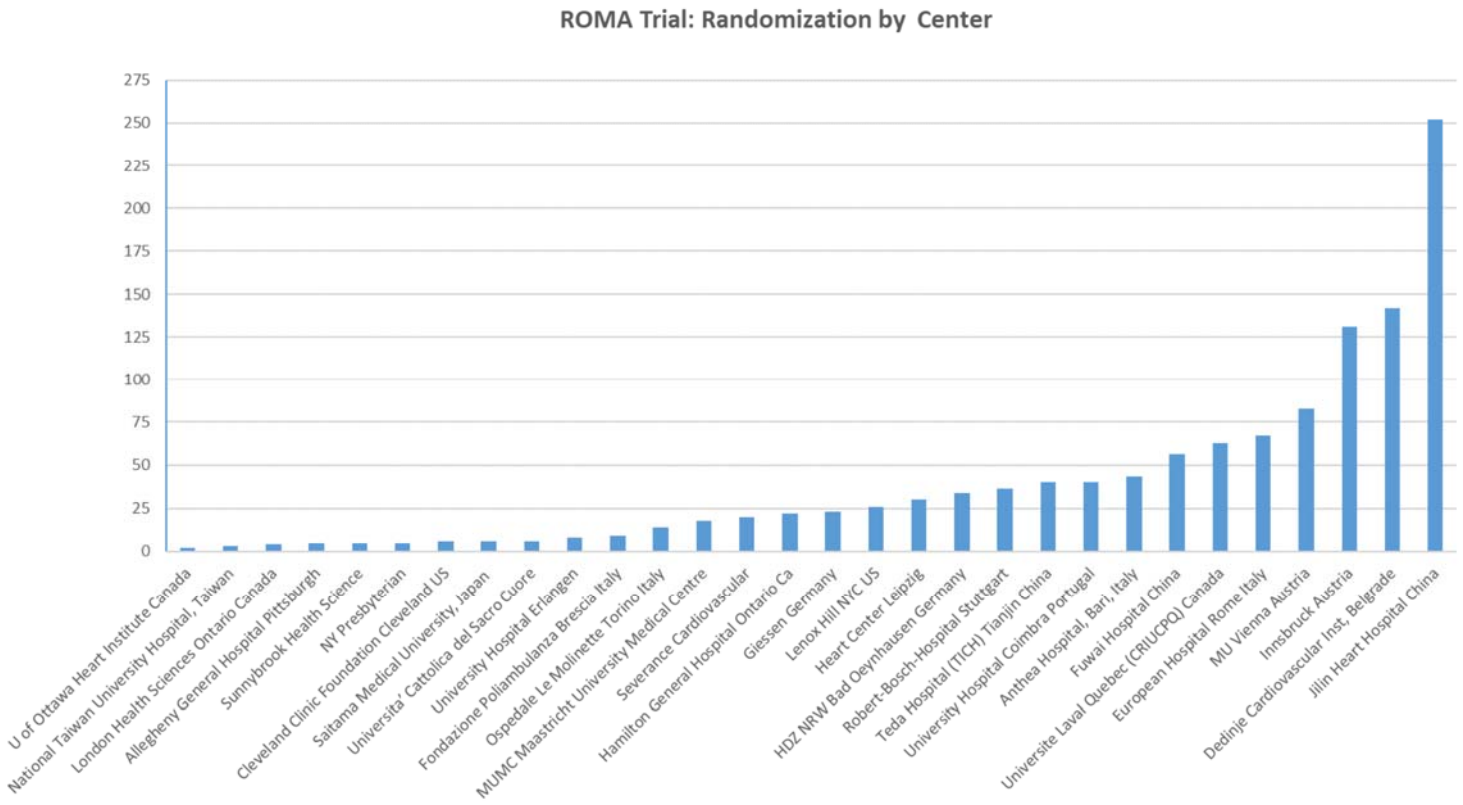
In light of some of the recent ethical breaches that have disrupted public confidence in the international research community we are resolved to standardize ROMA conduct to ensure our impact and provide translational results above reproach. This type of collaboration will have residual impact across all Investigator Initiated Trials conducted internationally. Thank you for working with us to develop best practices between diverse cohorts, while respecting the autonomy of each countries' governing agencies.

Subject Enrollment Updates

Total Subjects enrolled: 1209







Case Report Form	Total	Complete (n=)	Complete %	Incomplete (n=)	Incomplete %
Eligibility / Randomization	1209	1209	100%	0	0%
Follow up [2-12 weeks]	1038	991	95%	47	5%
Follow up [6 month]	726	659	91%	68	9%
Follow up [12 month]	322	270	84%	52	16%

ROMA Participating Site Highlight:

Fondazione Policiclinico Universitario

“Agostino Gemelli”: Rome, Italy

Fondazione Policlinico Universitario “Agostino Gemelli”, based in Rome, is a major hospital of central Italy. The Cardiac Surgery department is one of the most developed of the whole structure, consisting of several connected Operative Units: the Cardiac Surgery ward, the Intensive Care Unit and the Operating Theatre, composed of three new high tech OR’s. There is a strong collaborative environment; not only with the Cardiology Department, but also between departments. We deeply value cooperation and foster a multidisciplinary approach to the patient experience.

The entire centre can confidently take advantage of the Heart Team’s vast experience as a key instrument to optimize the management of complex care issues. Due to the increased risk and the several comorbidities of our patients, we find that a collegial decision-making process is the best way to provide the correct treatment for every case.

Our team is composed of 11 surgeons, 9 cardiac Surgery residents, 3 cardiologists and 12 cardio-anaesthesiologists; in addition to nurses, perfusionists and other allied healthcare professionals working towards the same goal; better outcomes and life quality for our patients.

ROMA Participating Site Highlight:
Fondazione Policiclinico Universitario
"Agostino Gemelli": Rome, Italy

We perform about 800 operations per year, both elective and urgent. Most of them are coronary artery bypass grafting, conducted both with extracoropreal circulation or off-pump. We also treat a high number of heart valve diseases, by replacing or repairing the injured valve; if possible, we prefer a minimally invasive approach, due to its evident advantages in terms of recovery, pain reduction and patient satisfaction. We also treat ascending aorta pathologies, congenital heart diseases, heart tumors, pericardial diseases, emergency procedures and many others. We can also take advantage of the new Hybrid Operating Room, opened in 2014, equipped with advanced medical imaging devices that enable minimally invasive surgery and hybrid procedures.

Thanks to precise preoperative and periopeartive care, a multidisciplinary approach and advanced technologies, we have achieved better mortality and morbidity outcomes. Our commitment to clinical research and industry improvement is an essential part of our daily practice and work culture.

We are honoured to take part in the ROMA trial and to collaborate with you all!

Work Flow Tips

Some of the major challenges long term studies encounter such as loss to follow up, incomplete data sets, and increasing time demands can be managed with proper planning

Retention techniques

I. **Set realistic expectations with subjects at time of enrollment:**

- The informed consent process is critical to allow subjects the opportunity to evaluate their desire to participate in a longitudinal study. Please thoroughly **evaluate the subjects commitment to at least 10 years of follow up, occurring every 6 months.**

- If potential subjects are not compliant in other areas of their heath care *they may not be ideal candidates for a long term study.*

II. Fostering resilient relationships with your ROMA participants:

- Update contact information at every contact and discuss possible follow up barriers

- Subjects who feel like an integral part of the study are more likely to engage long term. Remind your participants their role crucial towards the betterment of society while also appreciating their personhood during consent process and follow up calls.

- *Keep your current participants involved!* Many participants take personal pride in their contribution to science and medicine. Offer study information upon enrollment. Available at ***Clinicaltrials.gov/ct2/show/NCT03217006***

- Sending correspondence during major life events (birthdays, hospitalizations, deaths) can keep help build a community that lasts long term.

III. Be practical in planning follow-up contact with patients

- Try to minimize inconvenience when engaging our diverse study population. Some participants are busy and have a greater medical literacy. Others may need extra time to communicate their medical events. Use your current patient relationship when developing approaches to follow up.

Managing follow ups visits: Reporting Follow-up

In an effort to provide sites with real time monitoring information the following reports are now available to you in the Clinvestigator Database:

- ◊ Patients without Intraoperative Data
- ◊ Show Follow ups
- ◊ All Forms by Timepoint
- ◊ Enrollment / Randomization report
- ◊ Adverse events
- ◊ Randomization by month
- ◊ Randomized Patients without Consent Forms

See Appendixes for more information on each form

Something not available on any of these reports? Please reach out to us!

Data Integrity

Completing follow up on schedule may become challenging as enrollment grows. In our efforts to monitor the performance and data integrity we will be reviewing data completion ratio's on a biweekly basis. Please make your best efforts to:

- ♦ Enter collected data into Clinvestigator as close to the collection date as possible
- ♦ Ensure the expected CRF's are **completed** by their expected window
- ♦ We are in the planning stages of creating automated periodic email notifications from within the Clinvestigator database to:

1. Remind you of subjects that are approaching their next follow up window
2. Alert your of subject with eCRF's that have not been completed and are late

Sites that consistently do not complete follow up forms in a reasonable timeframe will be CLOSED to enrollment

Adverse Event Reporting

ROMA is considered an event driven trial. Your diligence in reporting them and supplying source documents in a timely manner is very important to the studies success. All events should be reported as soon as you become aware of them.

I. Serious Adverse events **MUST** be reported to us within 24 hours of notification

II. The SAE eCRF **MUST** be completed in the database when an event occurs. This triggers the notification to the study team.

If you only fill out event forms, we will NOT be notified.

III. Source documents are requested based on event type and are expected to uploaded within 10 days of initial coordinating center request

IV. Source documents requested by event can be found in **Appendix 4**

- ◊ All names, medical record numbers, and other sensitive information should be crossed out
- ◊ For all non English source documents: An English synopsis of the event should accompany all source documents
- ◊ Please be as detailed as possible in your descriptions of the event. Include information about chief complaints, history, evaluations, diagnosis and treatments for each event. This will help us prepare for the event adjudication and minimize the need for further follow up.
- ◊ Source documents should be named as clearly as possible and refer to the events name or term

V. Serious Adverse Events **should not be reported as a Protocol deviation**

VI. Serious Adverse Events should be reported to your local ethics and safety committees as mandated by your institution.

Maintaining Regulatory Compliance

- Site are responsible for maintaining regulatory approval for ROMA per their institution
- Please forward all renewal documents to ROMA@med.cornell.edu upon approval.
- Sites that require IEC/IRB renewal will receive an email from the WCM Coordinating requesting an update before the expiration date.

Protocol Non Adherence

Protocol Non Adherence and Crossovers are being closely monitored

- Protocol Non-adherence should be reported in the Intraoperative eCRF (*Question 6)* within 24 hours of the event
- Please attempt to complete the Intraoperative eCRF as soon as possible after surgery as this is where we capture protocol non adherence
- You will receive a follow up email from us to categorize the protocol Non Adherence as either a True Crossover or a protocol deviation *(see below)*

Crossover

- True Crossovers are when a subject was randomized to one arm but received the other
- Practice diligent preoperative assessments to minimize crossover events.
- Patients who are not candidates for one of the ROMA arms due to conduit quality should not be considered for enrollment

Protocol Deviation

- Planned conduits or targets were not used, but randomization arm was conserved
- All Protocol Deviations (including crossovers) should be reported on the Biweekly Protocol Deviation log. **This log should be sent even when new deviations have not occurred**
- Protocol Deviations should also be reported to your IEC/IRB per institutional guidelines

Ensuring Good Clinical Practices

Informed Consent Forms

While harmonized standards are being developed between the ICH-10 governed sites and GCP we request that the following are adopted by all of our sites for ROMA related activities:

- **Signing Informed Consent form:**
  - The subject signing the consent forms MUST sign, date and write the print name.
  - The person obtaining the consent should not date or write the print name for the subject
  - The informed consent form should be current, not expired
  - The person obtaining the consents MUST also sign, date, and print their name

- **Redacting Informed consent form (Appendix 2):**
  - The consent form should be redacted to remove any PHI (Protected Health Information).
  - The first and last initials and date of signature should be visible for verification purposes.
  - We recommend the use of Acrobat Pro for the de-identification of the PHI.

- **Uploading Informed consent form:**
  - The entire consent form -OR- first, last and signature pages must be uploaded
  - The Informed Consent form (ICF) MUST be uploaded prior to subject randomization.
  - The subject name should reflect the first and last initial of subjects names
  - The ICF upload name and document must not contain any PHI
  - ICF uploads can not be removed or changed by sites

  To change the ICF email ROMA@med.cornell.edu with the PID and a rational for the removal. Please allow 1 day from request to upload a new ICF.

- **Best Practices for documenting changes on paper:**
  1. Strikethrough the information you wish to change, leaving it visible :~~**Strikethrough**~~
  2. Write in the corrected information clearly, **then date and initial the correction**

Overall Long Term Study Development:

Year 2 Objectives

We respect the unique workflows at each site and are proud to support you in your everyday research activities. We will begin sending periodic emails with monitor feedback on the following items to assist in study management:

I. CRF completion/upload to Clinvestigator

II. Proper ICF redaction techniques and documentation of informed consent

III. Serious Adverse Event Reporting

IV. Regulatory compliance inquiries and attestation of following Good Clinical Practices

How can our monitoring efforts be made most useful to your site?

We realize that many of our team members work tirelessly as providers, researchers, and allied health professionals. If you find that there are significant challenges at your site delaying the completion of these requests please reach out to us.

We would also like to hear from you with feedback on how to best distribute these emails.

The WCM ROMA team ultimately functions as both monitor and support to our counterparts.

We will make every effort to help your site succeed.

We are happy to schedule a virtual meeting or call to discuss challenges in complying and to clarify any of the attached procedures. Please do not hesitate reach out to us to begin a dialogue toward fostering our mutual success!

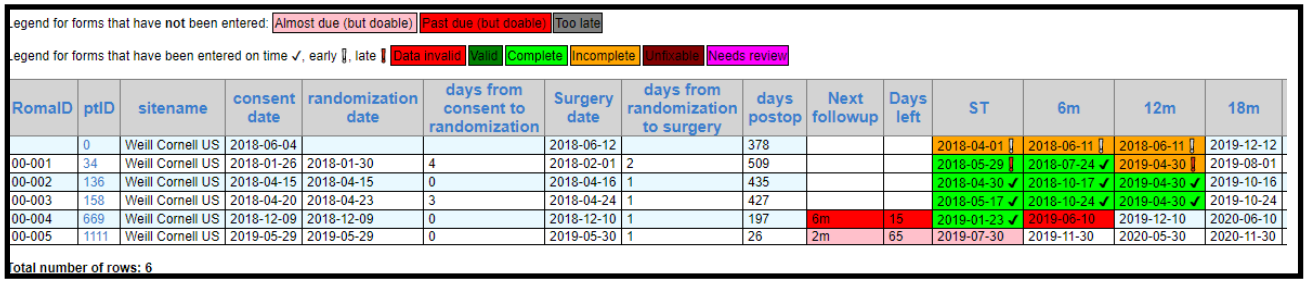
Thank you all for your valuable time, energy, and dedication.

Appendix 1

Show Follow Ups Report

This scheduling report allows you to manage Long Term Follow up visits. Use this report to target subjects that are nearing their ideal collection date. *It is also available as .csv file*

Clinvestigator View



Legend for forms that have **not** been entered: Almost due (but doable) | Past due (but doable) | Too late

Legend for forms that have been entered on time ✓, early ▯, late ▮: Data invalid | Valid | Complete | Incomplete | Unfixable | Needs review

RomaID	ptID	sitename	consent date	randomization date	days from consent to randomization	Surgery date	days from randomization to surgery	days postop	Next followup	Days left	ST	6m	12m	18m
	0	Weill Cornell US	2018-06-04			2018-06-12		378			2018-04-01 ▯	2018-06-11 ▯	2018-06-11 ▯	2019-12-12
00-001	34	Weill Cornell US	2018-01-26	2018-01-30	4	2018-02-01	2	509			2018-05-29 ▮	2018-07-24 ✓	2019-04-30 ▮	2019-08-01
00-002	136	Weill Cornell US	2018-04-15	2018-04-15	0	2018-04-16	1	435			2018-04-30 ✓	2018-10-17 ✓	2019-04-30 ✓	2019-10-16
00-003	158	Weill Cornell US	2018-04-20	2018-04-23	3	2018-04-24	1	427			2018-05-17 ✓	2018-10-24 ✓	2019-04-30 ✓	2019-10-24
00-004	669	Weill Cornell US	2018-12-09	2018-12-09	0	2018-12-10	1	197	6m	15	2019-01-23 ✓	2019-06-10	2019-12-10	2020-06-10
00-005	1111	Weill Cornell US	2019-05-29	2019-05-29	0	2019-05-30	1	26	2m	65	2019-07-30	2019-11-30	2020-05-30	2020-11-30

Total number of rows: 6

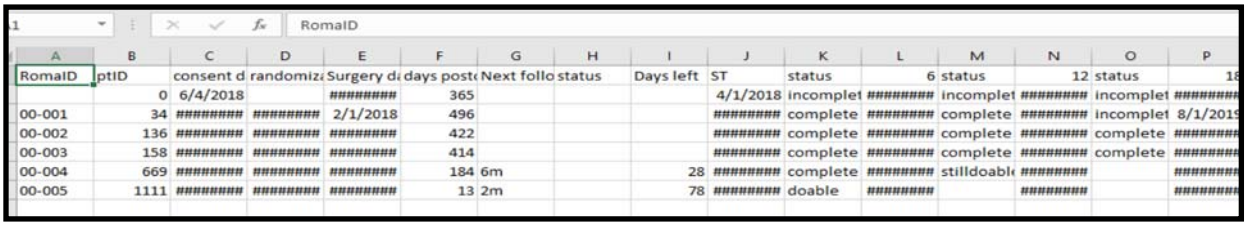
◊The date within the cell corresponds to the ideal date of collection, based on surgery date

◊The "**days left**" column indicates the absolute number of days to ideal date of collection

The color of the Long Term FU eCRF cell indicates its status as per the legend:

- White background - Not yet in the follow up window, no action required
- Pink background - Within the -30 day (before) window to the ideal date of follow up. The status of this form is considered "Almost doable" per the legend above and .csv below
- Red background - Within the +30 day (after) window to the ideal date of follow up. The status of this form is considered "Still doable" per the legend above and .csv below
- Grey Background - Outside of the -/+ 30 day window. Contact subject immediately as the window is outside of protocol guidelines. The status of this form is considered "Missing" per the legend above and .csv below

Excel View



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	RomaID	ptID	consent d	randomiz	Surgery d	days post	Next follo	status	Days left	ST	status	6	status	12	status	1
		0	6/4/2018		########	365				4/1/2018	incomplet	########	incomplet	########	incomplet	########
	00-001	34	########	########	2/1/2018	496				########	complete	########	complete	########	incomplet	8/1/201
	00-002	136	########	########	########	422				########	complete	########	complete	########	complete	########
	00-003	158	########	########	########	414				########	complete	########	complete	########	complete	########
	00-004	669	########	########	########	184	6m		28	########	complete	########	stilldoabl	########		########
	00-005	1111	########	########	########	13	2m		78	########	doable	########		########		########

Sites that consistently do not complete follow up forms in a reasonable timeframe will be CLOSED to enrollment.

Appendix 2

Other Reports

A. Patients *without* Intraoperative Data Report: Indicates subjects that have an incomplete or missing Intraoperative Form. *Available as .csv*

Patients without Intraoperative Data

ptID	sitename	randomizationdatetime	Did patient go to surgery	dateofsurgery	incomplete or missing
0	Weill Cornell US		Yes	2018-06-12	incomplete

B. All forms by timepoint: This report shows eCRF entries by subject

Patient coverage by timepoint and form

ID	Name (site)	Baseline				Post-Op / Discharge		2-12 weeks Follow-up		6 Month Follow Up		12 Month follow up		18 Month Follow-up	
		randomization	preoperative	intraoperative	medication	postoperative	medication	followup	medication	followup	medication	followup	medication	followup	medication
1	H, L (3)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		

C. Enrollment / Randomization Report: Shows details including dates of randomization and Study Arm by subject. *Available as .csv*

Randomization report

Site	stratum	ID	PID	Patient last name	Patient first name	Randomized by	When Randomized	Study arm
Innsbruck Austria	1	1	01-001	H	L	Ruttmann-Ulmer, Elmede	2018-01-07 08:44:41	Single

D. Adverse events: Lists SAE details by site for adverse events with completed SAE eCRF's. *Available as .csv*

	A	B	C	D	E	
1	Subject	PID	Sitename	Date created	Date of event	SAE diagnosis
2	0	00-000	WCM	5/17/2018	4/21/2018	Myocardial Infarct

Appendix 3

Redacted / Crossed-Out Informed Consent Form

Consent for Research Study

Project Title: Randomized comparison of the clinical Outcome of single versus Multiple Arterial grafts: the ROMA trial

Principal Investigator: Mario Gaudino, M.D.

RESEARCHER'S STATEMENT

I have fully explained this study to the subject. As a representative of this study, I have explained the purpose, the procedures, the benefits and risks that are involved in this research study. Any questions that have been raised have been answered to the individual's satisfaction.

Signature Signature SIGNATURE SIGNATURE 3/25/2019

Signature of person obtaining the consent (Principal Investigator or Co-investigator) | Print Name of Person | Date

SUBJECT'S STATEMENT

I, the undersigned, have been informed about this study's purpose, procedures, possible benefits and risks, and I have received a copy of this consent. I have been given the opportunity to ask questions before I sign, and I have been told that I can ask other questions at any time. I voluntarily agree to participate in this study. I am free to withdraw from the study at any time without need to justify my decision. This withdrawal will not in any way affect my future treatment or medical management and I will not lose any benefits to which I otherwise am entitled. I agree to cooperate with Mario Gaudino, MD and the research staff and to inform them immediately if I experience any unexpected or unusual symptoms.

A[redacted] A[redacted] A[redacted] A[redacted] 3/25/19

Signature of Subject | Print Name of Subject | Date

Signature of Legally Authorized Representative and Relationship to Participant (When Appropriate) | Date

Appendix 4

Source Documents by SAE

Source documentation requested to support Adverse Events

Please use this list as a reference tool to know which source documentation are required when reporting one of the following adverse event.

Death	1. Chart, consultation and discharge reports 2. Clinical/nursing notes 3. Autopsy report (if applicable)
Repeat revascularization (PCI or CABG)	1. Pre-procedure ECG 2. Post-Procedure ECG 3.Laboratory reports (cardiac enzymes) 4. Cath report 5. Operative report 6. Chart, consultation and discharge reports 7. Autopsy report (if applicable)
Myocardial Infarction	1. Chart, consultation and discharge reports 2. Laboratory reports (cardiac enzymes), ECGs 3. Angiogram 4. Echocardiogram 5. Clinical/nursing notes 6. Autopsy report (if applicable)
Stroke	1. Chart, consultation and discharge reports 2. Imaging (CT and/or MRI head scan) report(s) 3. Clinical/nursing notes 4. Autopsy report (if applicable)
Surgical site infection	1. Chart, consultation and discharge reports 2. Laboratory report(s) 3. Imaging/x-ray report(s) 4. Surgical notes 5. Clinical/nursing notes
Pericarditis	1. Chart, consultation and discharge reports 2. Echocardiogram 3. ECG

Important Study Reminders and Announcements

CONTACT US

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CCIMsupport@med.cornell.edu

Contract & Budget Inquiries:

JCTOcontracts@med.cornell.edu

Announcements

- Four new sites have joined the ROMA Collective since our March edition. Please Welcome:

London Health Sciences Centre - Ontario, Canada

Allegheny General Hospital - Pittsburg, PA, USA

Universita' Cattolica del Sacro Cuore - Rome, Italy

University of Ottawa Heart Institute - Canada

Congratulations

- Congratulations to Silvia Senese of Weill Cornell on the birth of her son. Welcome to the ROMA family, Baby Max!
- Congratulations to Efstathia A Mihelis of the Lenox Hill ROMA team on her recent promotion!
- ROMA was mentioned in the 2018 ESC/EACTS Guidelines on myocardial revascularization[1]. See below:

15.3 Gaps in the evidence

The role of FFR and iwFR in guiding surgical revascularization needs further investigation into whether it improves clinical outcomes. Likewise, there are insufficient data on the impact of intraoperative assessment of graft flow on outcomes.

In view of the limitations of observational studies comparing BIMA with SIMA and the limitations of the ART trial, the ROMA (Randomization of Single vs. Multiple Arterial Grafts) trial is recruiting to answer the question of whether the use of additional arterial conduits (either BIMA or radial artery) translates into superior clinical outcomes when compared with SIMA supplemented by SVG only.

Hybrid procedures, which combine minimally invasive arterial grafting with PCI, proved feasible and safe. However, multicentre studies are required to prove the efficacy and superiority of this approach in stable, multivessel coronary disease.

What's new at your site? Please send us information on local accomplishments, collaborative opportunities, and news of interest. **We want to hear from you!**

1. 2018 ESC/EACTS Guidelines on myocardial revascularization. Sousa-Uva M, Neumann FJ, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. Eur J Cardiothorac Surg. 2019 Jan 1;55(1):4-90. doi: 10.1093/ejcts/ezy289.