BEST-CLI – Happy Holidays 2017!

From the Desktop of Dr. Matt Menard: Important Protocol Changes highlighted & thoughts on trial burden.

Woohoo! – as Sandi Siami, our NERI Data Coordinating Center PI, is fond of saying. We are thrilled to have motored well past the halfway mark of BEST-CLI enrollment, a testament to the hard work of all of you participating in the trial. On our Thanksgiving Day list of the many things we are thankful for are the collective efforts responsible for this impressive achievement.

As you can all well imagine, there are myriad challenges in completing a clinical trial of the magnitude of BEST-CLI. We must balance obtaining valued data with the dampening effect of undue burden. We must navigate appropriately addressing the recommendations of the NIH and our DSMB (an independent oversight committee of experienced trialists tasked with overseeing the safety of BEST subjects and keeping the trial conduct proper) with sensitivity to the real challenges faced by nearly 160 trials sites and 900 individual investigators. We are well aware BEST-CLI compensates you all less than many industry-sponsored studies, and we have throughout tried hard to navigate this balance to the best degree possible.

As many of our veteran sites and colleagues will remember, we undertook a significant protocol revision two years ago, modifying what we thought were unduly burdensome exclusion criteria, increasing the amount of money sites received for each patient enrolled, and adding money for a stipend for each patient visit. We believe this amendment was successful, driving better enrollment and, in sum, worth the hassle to each of you to enact it.

Several month backs, we rolled out a set of questions on smoking behavior of patients enrolled into the trial. No doubt we could have done better - we gave little notice, provided no additional funding, and perhaps not surprisingly, got a fair measure of pushback. This led us to revisit, in a broader discussion and with close scrutiny, trial site burden in general – turns out, a topic of particular interest to our DSMB. Once again, we reviewed all aspects of the trial protocol and considered a number of potential changes, each on a metric of benefit vs burden. We had three inter-related goals: to enhance enrollment, to make the process of screening and enrolling CLI patients as painless and fruitful as possible, and to reduce trial-related burden on investigators, coordinators and participating trial sites wherever possible.

Here is what we decided to do, which will form the backbone of a new protocol amendment we will aim to roll out in Q1, 2018.

1. **Replace the lengthy, burdensome (and unpopular) originally-proposed smoking question-set with two succinct questions to be asked at trial closeout.** These questions will assess smoking behavior of enrolled patients during their time in the trial, data we have not previously been capturing.
2. **Remove the requirement for a diagnostic angiogram prior to randomization.** As currently structured, if a patient has significant tibial disease (to a degree requiring treatment to successfully address the CLI), an investigator cannot randomize that patient based on CTA or MRA alone but must first obtain a formal contrast angiogram. In recognition that times have changed, and given a) the quality improvements with CTA, MRA and duplex since the time of initial trial design, b) the fact that a number of investigators routinely take patients for revascularization based on CTA, MRA or even duplex outside of the trial and c) the requirement to obtain a formal angiogram is an undue burden for some (particularly, e.g., our Canadian colleagues who typically rely heavily on CTA and who cannot always obtain an angiogram in a timely fashion), **we will allow randomization based on CTA, MRA or duplex**. **Consistent with BEST-CLI pragmatic design, this decision will be left to each investigator's discretion going forward. Of note, we will continue to mandate contrast angiography if the infrageniculate anatomy cannot be adequately defined with less invasive imaging.**
3. **Remove the requirement that patients with tissue loss/gangrene must satisfy the current hemodynamic definition of CLI,** for cases in which an investigator believes a patient has CLI based on clinical and anatomic grounds but has difficulty documenting any of the hemodynamic criteria. The requirement will remain as is for patients with ischemic rest pain.
4. **Increase the stipend each patient receives at each patient visit from $25 to $50. For patients who have an undue travel burden, the payment will be increased to $100.** While undue travel burden is primarily intended to apply to patients traveling over 100 miles, this enhanced stipend will be considered for others on a case by case basis.
5. Responsive to a DSMB directive to better capture information on the contralateral limb (given concerns for treatment bias), **add several succinct questions at trial closeout to collect contralateral amputation and (limited) revascularization history**.
6. **Enable centralized and long-term follow up of enrolled patients**. Another recommendation from our DSMB, this will be an invaluable mechanism to enhance data collection for patients otherwise considered lost to follow up.
7. We gave serious consideration to reducing the degree of required SAE reporting. After detailed review, we ultimately felt the benefit from SAE documentation as currently structured was too valuable – not just for capturing end-point events and cost-effectiveness analysis but for other aspects of the trial as well -- to justify modification.

*Article continued on page 5.

Funded by: NIH National Heart, Lung, and Blood Institute

Site Spotlight

Site #1156 / Minneapolis VA

Pictured above (starting with back row): Dr. Steve Santilli, Dr. Daniel Ihnat, Dr. Paul Orecchia, Dr. Derrick Green, Carolyn Robinson, NP, Sandra Price, RN, and Mary Kerr, NP.

Pictured Above: Study Coordinator, Catherine Dowse

The Minneapolis VA Health Care System (VAHCS) is a very busy place. VAHCS is a teaching hospital providing a full range of patient care services with state-of-the-art technology, as well as education and research. We are a regional facility that draws our patients from a five state region and serves veterans residing in the states of Iowa, Minnesota, Nebraska, North Dakota, South Dakota and portions of Illinois, Kansas, Missouri, Wisconsin and Wyoming.

The secret to our enrollment success is largely due to the age of the patients that are seen. A large majority are older, former smokers or diabetics, making this a prime location to find CLI candidates. We have a wonderful team that works together to make sure that we do not miss an opportunity to talk to any potential study participant. Communication between the staff and the patient is essential. We have only been active in the study since December and have already enrolled four with two others that did not pass beyond the screening phase. We may be young within this study but we are willing to give it our all for our veterans. We are proud to participate in this important study that will affect so many in the future.

Q4 2017 Site Payments Data Freeze Approaching!

The data freeze for the next round of site payments is scheduled for **December 31, 2017**.
Be sure to enter your data and respond to queries in eCOS to ensure proper payment!

Have questions regarding site payments?
Please send them to BEST@neriscience.com.

November Top Enrollers 2 subjects each!

1029 / Michael E. DeBakey VA

1217 / Univ. California, Davis

1351 / KPNCAL

British invade hugely inspirational Investigators Meeting at VEITH!

We had a highly successful Investigators meeting at VEITH. Not since the British rock invasion of the 60's has there been such an influence on US soil. But more on that anon. After an update of the trial by Alik Farber and Matt Menard (Kenny was busy dancing at his son's wedding) on all things buzzing in the world of BEST, David Dexter from Sentara Vascular, Igor Laskowski from Westchester Medical Center and Sudhir Nagpal from Ottawa Hospital got us started with eloquent testimonials as to how they have been so effectively knocking it out of their respective ballparks. Each had a unique twist on overcoming common barriers, and engaging all members of their team to successfully randomize at a steady clip. Each was an impressive call to arms as to how it can be done, and done well.

Roger Greenhalgh, one of the grandmasters of European vascular surgery, gave an extended inspirational perspective on trial dynamics and psychology. Presenting earlier at the VEITH meeting on the 15-year follow up of both EVAR-1 and EVAR-2, he knows a thing or two about large randomized trials. Keep the faith, and believe in your mission – his advice certainly timely to all of us in the trenches of BEST. Alison Haliday, the PI of ACST1 and currently running her own marathon with ACST2, offered her similar insights into the importance of large clinical trials and strategies to combat trial fatigue. Finally, Andrew Bradbury gave his usual inspirational perspective on the parallel efforts of BEST and BASIL -2 and -3, and the power the eventual combined data-set will have to provide much-needed Level 1 data for the CLI population.

Peter Gloviczki provided a unique view on the power of BEST-CLI to set an example for future trialists, and to send a message to the NIH of what those dedicated to the goal of high-level RCT data can partner to achieve. As an esteemed member of the SVS and as co-editor of the JVS, Peter generously pledged ongoing support of both organizations in helping to drive the mission of BEST-CLI forward. Michael Conte, Co-Chairman of the BEST-CLI Executive Committee along with Chris White, put BEST-CLI in context as to where we are with CLI treatment at this moment in time: there is much to do, between educating a public largely unaware of the perils of PAD, to focusing the energy of the medical community just beginning to grapple with the global epidemic of CLI, to ensuring that all those that care for CLI take ownership of BEST and help bring this important trial to a successful completion. To conclude, we had a rousing panel discussion with all of the coordinators whose sites met the enrollment challenge of last summer. Panelists included Emma Schlueter from the San Diego VA, Sarah Barbey from the University of Florida, Gainesville, Deanna Garcia from New Mexican Vascular Institute, Diana Kim, from UCSF, and Thomas Cheng from perennial front runner Boston Medical Center (unfortunately the coordinator from Loma Linda MC, Vanessa Miller, could not make the trip to VEITH).

Alik, Kenny and I pretty much always come from these meetings refreshed, and newly inspired in our quest to summit the formidable slopes of BEST CLI. Many thanks to all who attended, and for those who could not, hopefully you can sense and absorb the inspiring words that were offered to all those who understand the importance of this landmark trial and who are working hard to see it succeed.

- *Matthew Menard, MD*

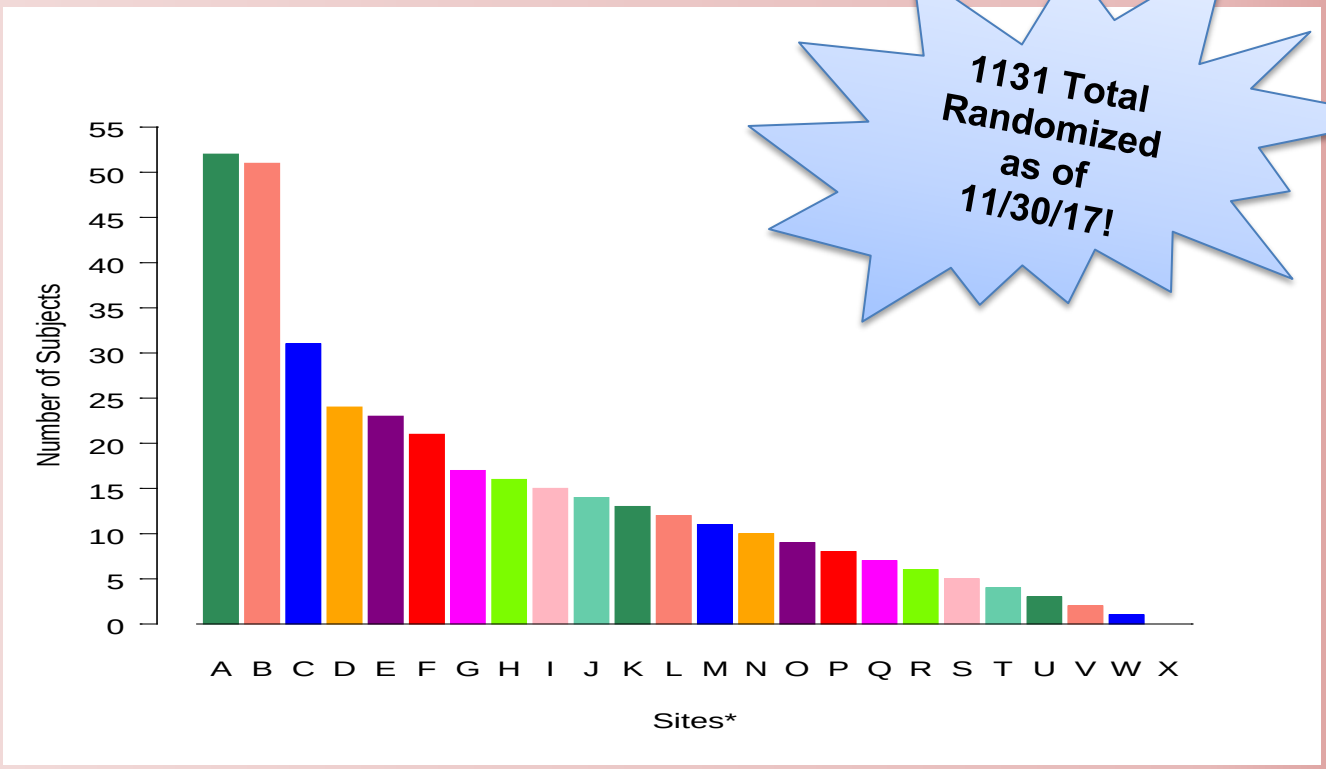
Principal Investigator Dr. Alik Farber leads a discussion with the Site Coordinators who won the Summer Fun Enrollment Challenge - and thanks them for their hard work!

Principal Investigators Menard and Farber discuss the trial with Dr. Michael Conte, Diana Kim, Dr. Andrew Bradbury (BASIL) and Dr. Roger Greenhalgh

Coordinators Deanna Garcia, Sarah Barbey, Thomas Cheng, and Emma Schlueter discuss enrollment experiences

Funded by: NIH National Heart, Lung, and Blood Institute

Enrollment Leaderboard



Sites*

A: 1160 - Keck MC of USC

B: 1258 - Boston MC.

C: 1238 - Univ. of Massachusetts Medical School

D: 1154 – Yale.; 1273 – Univ. of Florida (Gainesville); 1274 – Univ. of Oklahoma Health Sciences Ctr.

E: 1309 - Mercy Hosp. MC/ Iowa Heart

F: 1009 - Dartmouth Hitchcock MC; 1260 - Greenville Memorial Hosp.; 1284 – Chu de Quebec.

G: 1005 - Brigham and Women's Hosp.; 1261 - Indiana Univ. Medical School;

H: 1105 - Medical College of Wisc.; 1272 - St. Boniface Gen. Hosp.; 1288 - Kaiser Hosp.(Hawaii).

I: 1041 - San Francisco Veterans Affairs MC; 1282 - Carondelet Heart & Vascular Institute;

J: 1101 - Albany MC; 1281 - VA Western NY Healthcare System; 1352 - San Diego VAMC.

K: 1017 – Henry Ford Hosp.; 1104 - VA Palo Alto

L: 1013 - Harbor-UCLA MC; 1125 – UCSF MC; 1217 – UC Davis MC; 1276 - Memorial Hermann Hosp.

M: 1055 - Mount Sinai MC; 1108 - Michigan Heart Hosp.; 1113 - Oregon Health and Science Univ.; 1256 - BIDMC; 1279 - North Carolina Heart and Vascular Research; 1290 - Loma Linda Univ. MC; 1318 – UNC Hosp.; 1342 – Regina Qu'Appelle; 1367 - Englewood Hospital and Medical Center.

N: 1066 - Arizona Heart Hosp.; 1095 - Johns Hopkins Hosp.; 1135 - Univ. of Pittsburgh MC; 1275 - MUSC; 1323 – Univ. of Nebraska MC; 1332 - Denver VAMC; 1346 – Gundersen Health System.; 1351 – KP NCAL.

O: 1030 - Montefiore MC; 1061 - Baptist Hosp. of Miami; 1305 - Univ. of Virginia; 1310 - Harborview MC; 1311 - Dallas VA MC; 1340 – Wake Forest Baptist Hosp.;

P: 1010 - Emory Univ.; 1306 – McGill; 1308 - The Ohio State Univ.; 1374 - Westchester MC Health;

Q: 1075 - Swedish MC; 1140 – Greater Los Angeles VA; 1169 - Case Western Reserve; 1173 – SUNY Upstate; 1234 – Univ. of Toledo MC; 1259 - Rhode Island Hosp.; 1277 - The Univ. of Utah; 1293 - Univ. Health System; 1314 - VA Boston Healthcare System; 1344 – Michigan Vascular Center; 1348 – New Mexico Heart Institute; 1359 – The Ottawa Hospital.

Enrollment Leaderboard Continued

R: 1003 – Alleghany General Hosp.; 1018 - Inova Fairfax Medical Campus; 1023 – Massachusetts General Hosp.; 1026 - Medstar Washington Hosp. Center; 1029 - Michael E. DeBakey VA MC; 1046 - Steward St. Elizabeth's MC; 1072 - Univ. of Wisconsin – Madison; 1156 – Minneapolis VAMC; 1188 - Toronto General Hosp.; 1285 – Duke Univ.; 1337 – Loma Linda VA MC; 1345 – Los Angeles MC, Kaiser Permanente; 1349 – Queens Elizabeth II Health Science Center.; 1368 - Sentara Vascular Specialists;

S: 1054 - Univ. of Colorado Hosp.; 1134 - Univ. of Michigan Health System; 1263 - Kaiser Permanente (San Diego); 1264 - Minneapolis Heart Hosp.; 1271 - Southern Illinois Univ. SOM; 1300 - Tampa General Hosp; 1316 - Holy Name MC; 1325 - Deborah Heart and Lung Center; 1331 - Pinnacle Health System; 1347 – Maine MC; 1370 – Rutgers New Jersey Medical Center.

T: 1059 - The Univ. of Alabama; 1076 - Northwestern Memorial Hosp.; 1137 - The Univ. of Vermont MC, LLC; 1182 - Providence Heart and Vascular Institute; 1229 - Penn State Milton S. Hershey MC; 1292 – Munroe Regional MC; 1304 - CAMC Clinical Trials Center; 1326 - The Miriam Hosp.-Brown Medical School; 1334 – Stanford; 1350 - Benaroya Res. Inst. At Virginia Mason.

U: 1007 – Cleveland Clinic Foundation; 1008 – Columbia Univ. MC; 1019 - Jewish General Hosp.; 1024 – Mayo Clinic (Rochester); 1034 – Ochsner MC/Clinic Foundation; 1226 – St. Paul's Hospital (U. Saskatchewan); 1269 - Ohio Health Research Institute; 1270 - Scott and White – Temple; 1283 – Univ. of Oklahoma College of Medicine (Tulsa); 1294 - North Central Heart Institute; 1307 – Univ. of Rochester; 1320 - Portland VA MC; 1341 – Meriter Wisconsin Heart; 1355 - Vancouver General Hospital; 1357 – St. Francis Hospital; 1379 – Long Beach VAMC

V: 1257 - Univ. of Arkansas for Medical Services; 1278 – Univ. of California Irvine; 1287 - Providence Sacred Heart MC; 1301 – UCSD - Sulpizio Cardiovascular Center; 1302 – UCLA - Gonda Vascular Surgery; 1336 - Staten Island Univ. Hosp.; 1339 – Cadence Health (Chicago); 1356 - South Shore Hosp.; 1375 - West Haven VA (WHVA).; 1377 - Decatur Memorial Hospital.

W: 1116 - Rush Univ. MC; 1121 – Temple Univ.; 1126 - Univ. of Chicago Medicine; 1131 – Univ. of Maryland; 1151 - William Beaumont Hosp.; 1299 - Univ. of Tennessee MC; 1315 - George Washington Univ. Hosp.; 1354 - Durham VAMC; 1361 - Midwest Aortic Vascular Institute; 1369 – Milwaukee VAMC; 1376 - University of Western Ontario.

X: 1327 - Wellmont Holston Valley MC; 1358 - Vascular Health Partners, CCP; 1362 - Mount Sinai Medical Center (Miami, FL); 1364 – Sacramento VAMC; 1365 - Tampa VAMC; 1373 - Baton Rouge General Medical Center; 1382 – St. Louis VA

*Data frozen on 29/Nov/2017
**Site names abbreviated to conserve space

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As you have heard us say many times, the NIH has been extremely supportive of our efforts to bring BEST-CLI to a successful completion, and they are fully behind this renewed effort to reduce trial burden. Nevertheless, the push to hit our enrollment targets is real, and as important as ever. We need each of you, now as much as ever, to continue your hard work to enroll as many of your CLI patients into BEST as possible. We had an excellent Investigators Meeting at VEITH, and I will close by reiterating the challenge we posed to those in attendance – please do your best to bring in at least one patient every two months. That is 6 patients a year. We believe that is a realistic goal for each of you. Many thanks from all of us at BEST-CLI, and we hope those who celebrated it had a relaxing and enjoyable Thanksgiving.

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