Peripheral **R**eg**i**stry of Endovascular Clinical Outco**me**s

"The PRIME Registry"

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1. Background/Introduction:

Peripheral Vascular Disease (PVD) is an epidemic alarmingly on the rise and seriously impacting many individual's quality of life. It is estimated that 20% of patients >75 years will be living with the disease by the year 2030[(1)]. Critical Limb Ischemia (CLI), a serious form of PVD, is a severe blockage in the arteries of the lower extremities which markedly reduces blood-flow. CLI is a chronic condition that results in severe pain in the feet and toes and is commonly coupled with multiple co-morbidities, including, but not limited to, obesity, hypertension, diabetes, and increased age. With the increasing prevalence of PVD in an aging population, and the limitations of vascular surgery in patients with significant comorbidities, operators are gravitating more toward less invasive endovascular therapy. Endovascular therapy and vascular surgery have been proven equivalent in patients with CLI[(2)].

Patients with CLI can also progress to amputation. Amputations carry a poor prognosis with significant co-morbidity and mortality[(3)]. Also, there continues to be a significant variation in amputation trends across the United States depending on the patient's location. This is still the case despite the current evidence linking amputations to poor outcomes [(4)].

In an effort to categorize the anatomical properties of peripheral vascular lesions, the Transatlantic Inter-Society Consensus (TASC) divided peripheral lesions in four categories. This classification has been recently updated to TASC II[(5)]. The TASC classification however fails to address the complexity of infra-popliteal disease in critical limb ischemia patients. Depending on the patient population, tibial vessels tend to be diffusely diseased. With the increasing complexity of CLI patients, operators are tackling these lesions more frequently and successfully.

Endovascular revascularization of patients with PVD has evolved dramatically. New technology has arisen due to a better understanding of the atherosclerotic process. Treatment modalities encompass balloon angioplasty, stenting, and atherectomy. New modalities of therapy on the horizon include bio-absorbable stents and drug eluting balloons. However, data regarding the effectiveness of these modalities in infra-popliteal disease is scarce. A need exists for reporting on real world data, to document short and long term outcomes.

Metro Health has developed a peripheral vascular intervention program with the on-going goal of being viewed as a center of excellence in the prevention of CLI. In a quest to capture procedure-related details and outcomes related to these approaches, the team at Metro Health has developed an outcomes data registry to measure and report on minimally invasive endovascular therapies, to treat advanced PVD and CLI. Multiple institutions will collectively contribute data to the registry to advance the understanding of patient management and outcomes across all endovascular treatment modalities for advanced PVD and CLI.

2. Objectives:

The primary objective of PRIME is to systematically document endovascular revascularization approaches and patient outcomes with advanced PVD and CLI both in-hospital and at 1 month, 3 months, 6 months, and annually for 3 years following treatment. Secondarily, by collecting and summarizing data describing the management and outcomes of these patients, manuscripts will be generated with the goal of improving outcomes. Possible examples include:

- A decrease in the major amputation rate
- A decrease in complications associated with peripheral vascular interventions
- Improvements in the quality of life for patients with advanced PVD and CLI
- Development of mathematical tools to assess risk and outcomes
- Development of standardized testing methodologies
- Development of endovascular treatment guidelines
- Development of follow-up protocols for interventional patients with advanced PVD and CLI
- The promotion of evidence-based care models
- A reduction in the cost of treating patients with advanced PVD and CLI

3. Methods

Eligible patients with advanced PVD and CLI at medical centers participating in the PRIME Registry will be considered for enrollment in the PRIME registry. Patients will be asked to give consent within 30 days prior and 60 days post index procedure to participate. Once patients are are enrolled, their demographics, medical history, disease-relevant conditions, treatment details and outcomes will be collected for 3 years. Please refer to the initial and follow-up data form for variables collected in the PRIME registry database. Data collected meet the requirements of a “Limited Data Set” as defined by the United States HIPAA regulations. Data contain selected dates but do not include patient names, initials, or medical record numbers. Using web-based data entry this information will be placed into a secure password protected on-line database. Patients are identified in the database by a unique subject record number assigned sequentially by the electronic database and unrelated to their medical record number. This number will follow the patient for the duration of the study. These unique numbers can only be matched with patient identifiers by the individual site coordinator at each institution. It is up to the individual sites to keep a secure key linking the patient and the subject id number for accurate patient follow-up.

Oversight of the PRIME Registry is provided by a Steering Committee and Publications Committee. These committees are comprised of physicians from participating sites and the PRIME Coordinating Center. Decisions regarding protocol changes, investigator roles, addition or deletion of participating sites and publication of abstracts and manuscripts are made by these committees. Data used in abstracts and manuscripts is aggregate data only. No identifiable data is used.

Participant data will be stored in PRIME for an indefinite period of time. Participants will not be informed of the results of retrospective research studies involving the use of their information contained in PRIME.

4. Human Subjects:

Individuals to be approached for participation in PRIME will meet each of the following inclusion criteria:

a) Adult male and female patients ≥ 18 years of age.
b) Patients who are to receive or have received lower extremity endovascular intervention
c) Rutherford III-VI Classification
d) Ability to provide informed consent within 30 day prior to 60 days post endovascular intervention.
e) Ability to follow up at enrollment site.

Exclusion Criteria:
Inability or unwillingness to consent for participation in the registry.

Note: Since participation in PRIME does not involve a risk of physical harm, women of childbearing potential will not be queried as to pregnancy status or tested for pregnancy.

5. Recruitment Procedures:

Patients who meet eligibility criteria at participating PRIME centers will be invited to participate in PRIME. Unless otherwise approved, all consecutive patients will be enrolled each month. Due to the voluntary nature of this registry, sites may have limited resources. If all consecutive patients are not able to be enrolled, an alternate method of enrolling patients may be utilized, if used consistently and approved by the site's IRB and the PRIME Steering Committee. Some examples would be enrolling the first 5 or 10 eligible patients each month or enrolling only on odd numbered days. Although the recruitment process may vary by site, potential participants will be approached by a member of the research staff and will be asked to review a copy of the IRB-approved informed consent form. The research staff will review the consent form and address any questions or concerns prior to obtaining written informed consent for PRIME participation. The research staff will also address any future questions or concerns that may occur. To insure lack of selection bias, a screening log of subjects who meet eligibility criteria, but decline consent, will be kept at the site. A de-identified version of this list will be provided to the coordinating center on request.

6. Potential Risks of Research Registry Participation:

There are no risks of physical harm associated with participation in PRIME as this is an observational registry only and no treatment is added or dropped due to a patient's participation in the registry. Participation in PRIME does involve the potential risks of a breach of confidentiality of the medical record information and associated privacy of the participants. Such risks will be minimized by 1) removing direct participant identifiers (i.e., there will be no names, social security numbers, medical record numbers recorded); 2) placing recorded information on a secure server with limited access to information linking unique subject record numbers with direct participant identifiers; and 3) limiting access to the PRIME database to the appropriate IRB-approved staff at each site. Each user at a site will have his or her own log-on and password to access the database. Obtaining access to the database allows research staff the ability to enter patients' clinical data and to view their site's data. Site users are unable to access or view data from other sites.
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7. Potential Benefits of Research Registry Participation:

There are no direct benefits associated with participation in PRIME. However, the use of information contained within PRIME for retrospective analyses may be of future benefit to patients with PVD. Participants in PRIME will be informed of future research studies involving PVD for which they may be eligible if they so desire.

8. Costs and Payments:

All costs associated with the implementation and maintenance of PRIME shall be supported by Metro Health through institutional support and unrestricted grants from industry. No costs will be incurred by PRIME participants. Patients will not be remunerated for their participation in PRIME. Similarly, as this is a voluntary registry, sites will not be paid to participate in the registry.

9. Addition of PRIME Registry Sites:

Once the decision is made by the PRIME Steering Committee to add a new site, the Coordinating Center will communicate with that site to insure all regulatory documents are completed. PRIME Registry members are required to have active IRB approval and a signed data use agreement to participate in PRIME. Only after these documents are received by the Coordinating Center are users at each site issued log-ons and passwords for the database. Patient consent requirements are determined by each site's IRB. IRB approval must be updated regularly based on the schedule determined by each institution's review board. Sites that have not maintained IRB approval may not continue to add patients to the registry until their IRB approval is obtained.

In order to ensure data accuracy, periodic auditing of participating sites will be conducted. The PRIME Coordinating Center will receive de-identified source documents for the first five patients enrolled at each new center; additionally, documentation for subsequent patients may be requested if deemed necessary by the reviewers. Further adjudication may be performed at random intervals.

10. Statistical Design:

Coordinating Center statisticians combine data collected from all sites in aggregate tables. Only aggregate data is used in analysis. No identifiable data are used.

Continuous data shall be expressed as means +/-standard deviations or medians (Q1-Q3) as appropriate. Discrete data shall be expressed as counts and percentages. Chi-squared, Fisher's exact tests and student's t-tests may be used as appropriate to determine statistical significance. Linear and logistic regression and survival analysis may be applied to create statistical models.

11. Protocol References:

1. Shammas NW. Epidemiology, classification, and modifiable risk factors of peripheral arterial disease. Vasc Health Risk Manag 2007;3(2):229-34.
2. Forbes JF, Adam DJ, Bell J, Fowkes FG, Gillespie I, Raab GM, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Health-related quality of life outcomes, resource utilization, and cost-effectiveness analysis. J Vasc Surg 2010;51(5 Suppl):43S-51S.
3. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. N Engl J Med 2009;361(14):1368-75.
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5. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45 Suppl S:S5-67.

12. Database References:

1. Creager MA, Belkin M, Bluth EI, Casey DE Jr, Chaturvedi S, Dake MD, et al. Key Data Elements and Definitions for Peripheral Atherosclerotic Vascular Disease. J Am Coll Cardiol 2012;59(3):294-357.
2. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic). JACC 2006;47(6):1239-1312.
3. Mehran R, Rao SV, Bhatt, DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized Bleeding Definitions for Cardiovascular Clinical Trials. Circulation AHA 2011;123:2736-2747
4. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45 Suppl S:S5-67.