Form I: BTI Internship Program Mentor Application

A.1: Mentor information		
Name Tony Panzarella Assistant Professor	Institution University of Toronto	Department Public Health Sciences

A.2: Co-mentor information (if applicable)		
Name	Institution	Department

A.3: Research proposal (maximum two pages)

Title

Statistical design and analysis issues analyzing a phase III randomized clinical trial for the prevention of chronic graft-versus-host disease in cancer patients who have received an allogeneic bone marrow transplant from an unrelated donor

Background:

- Allogeneic bone marrow transplantation cures a wide range of hematological disorders; however, 40-60% of recipients are then exposed to increased morbidity and mortality and decreased quality of life from chronic graft-versus-host disease (GVHD) (1). We conducted a phase III randomized clinical trial to test the hypothesis that the addition of Thymoglobulin® (ATG) to the preparative regimen will result in a decrease in the proportion of patients with chronic graft-versus-host disease, resulting in improved quality of life but without an increase in mortality, disease relapse or death due to infection. The primary efficacy endpoint was freedom from systemic immunosuppressive drugs without resumption up to 12 months after transplantation. For this "focused stringent-positive" variation of chronic GVHD-free survival primary endpoint, death (or recurrent malignancy) before withdrawal of immunosuppression equated to failure in the sense that success cannot be attained, but death or recurrent malignancy after withdrawal of immunosuppression (before the 12-month time point for assessment) still counted as success. This approach sharpens the "focus" on chronic GVHD as outcome of greatest interest by not requiring the intervention to prevent death and recurrent malignancy after it has provided the benefit of preventing chronic GVHD. We recruited and assigned 203 eligible patients to treatment (101 to ATG and 102 to no ATG) using the dynamic allocation technique called minimization. Thirty-seven (37%) of 99 patients who received ATG were free from immunosuppressive treatment at 12 months compared with 16 (16%) of 97 who received no ATG (adjusted odds ratio 4·25 [95% CI 1·87–9·67]; p = 0·00060 (2). In a subsequent analysis, this statistically significant difference persisted at 24 months post-transplant (3).

Aims:

- Compare the efficiency of minimization, simple randomization, and stratified randomization in achieving a balanced allocation of treatment groups. We used minimization to achieve balance in our study. As the study is now complete, we can investigate what the allocation ratio would have been if we chose to use simple randomization or stratified randomization instead.
- Compare the results of our published trial with those we would have obtained had we used the more traditional endpoint, chronic GVHD-free survival. As the latter outcome is a composite endpoint defined as the first occurrence of chronic GVHD, recurrence or death (from any cause), an accompanying analysis will be performed to summarize their relative occurrence as the first event.
- Compare treatment groups ATG vs. No ATG for overall survival adjusting for quality of life (QoL)
- Identify predictors of our QoL secondary endpoints.
- Incorporate the method of multiple imputation for missing data to test the robustness of our conclusions with respect to QoL endpoints.
- Use R Markdown to enable an easily reproducible final report that interweaves the analysis code with

the results.

Methodology:
- Treatment groups will be compared for chronic GVHD-free survival using the Cox proportional hazards model. QoL endpoints were analyzed both cross-sectionally and longitudinally. Therefore, multiple linear regression and linear mixed model regression, respectively, will be used to identify predictors of QoL. Overall survival will be adjusted for quality of life using the Q-TWiST method (Quality Adjusted Time Without Symptoms or Toxicity). Rubin's multiple imputation procedure (4), which replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute, will be implemented.

Training Objectives:
- To identify advantages and disadvantages of stratified randomization and minimization
- To analyze time to failure endpoints using i) the Kaplan-Meier method and ii) the Cox proportional hazards model, and to test assumptions of this semi-parametric model
- To outline statistical issues involved in the design and analysis of composite outcomes
- Learn to distinguish missing data that is i) missing completely at random, ii) missing at random and iii) missing not at random.
- Describe the underlying process behind the method of multiple imputation and its advantages over single imputation methods
- To understand in what contexts adjustment for survival based on quality of life is relevant as a study endpoint
- Note: These training objectives will be met by setting weekly goals and holding regular meetings to discuss progress and issues encountered.

Environment:
- Located at the University of Toronto the Division of Biostatistics is part of the Department of Public Health Sciences within the Dalla Lana School of Public Health (DLSPH). The DLSPH (located at 155 College Street in downtown Toronto) is an internationally recognized community of scientists, teachers, students, practitioners, policy makers and citizens, creating new knowledge, educating change makers, advancing practice and guiding the way to better, more equitable outcomes in population health and health systems – locally, nationally and globally.

Intern background/strengths:
- Regression modeling experience, with an interest in survival analysis methods and randomized clinical trials. Experience with SAS/R is an asset.

OICR Strategic Plan:
- Randomized clinical trials provide valuable evidence to advance cancer treatment and prevention strategies. The randomized clinical trial described in this proposal was a collaborative effort between researchers in Canada, the United States and Australia. The results were presented at the American Society of Hematology and published in both *The Lancet* and *Lancet Haematology*. This effort was instrumental in changing clinical practice for cancer patients with leukemia and other hematological disorders who receive allogeneic hematopoietic stem cell transplants from unrelated donors. The trial sponsor was the Canadian Blood and Marrow Transplant Group, now the Cell Therapy Transplant Canada (CTTC). CTTC is a member-led, national, multidisciplinary organization providing leadership and promoting excellence in patient care, research, and education in the field of hematopoietic stem cell transplant and cell therapy. This network of collaborators, including strong representation from Ontario, is recognized in OICR's Strategic Plan as a key factor in promoting clinical trial design and planning.

- There is a paucity of statistical expertise in the field of hematopoietic stem cell transplants in Canada. This internship will provide valuable statistical training and help promote the application of this statistical knowledge to the design and analysis of trials, in general, and more specifically to diseases such as leukemia, lymphoma and multiple myeloma that depend on allogeneic hematopoietic stem cell transplants.

References:

(1) Boyiadzis M, Arora M, Klein JP, et al. Impact of chronic graft-versus-host disease on late relapse and survival on 7489 patients after myeloablative allogeneic hematopoietic cell transplantation for leukemia. *Clin Cancer Res* 2015; 21: 2020–28.
(2) Walker I, Panzarella T, Couban S et al. Pretreatment with anti-thymocyte globulin versus no anti-thymocyte globulin in patients with haematological malignancies undergoing haemopoietic cell transplantation from unrelated donors: a randomised, controlled, open-label, phase 3, multicentre trial. *Lancet Oncol*. 2016 Feb;17(2):164-173. doi: 10.1016/S1470-2045(15)00462-3. Epub 2015 Dec 24. Erratum in: Lancet Oncol. 2018 Nov;19(11):e581.
(3) Walker I, Panzarella T, Couban S et al. Addition of anti-thymocyte globulin to standard graft-versus-host disease prophylaxis versus standard treatment alone in patients with haematological malignancies undergoing transplantation from unrelated donors: final analysis of a randomised, open-label, multicentre, phase 3 trial. *Lancet Haematol*. 2020; 7: e100-e111
(4) Rubin, D.B. (1987), Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons, Inc.