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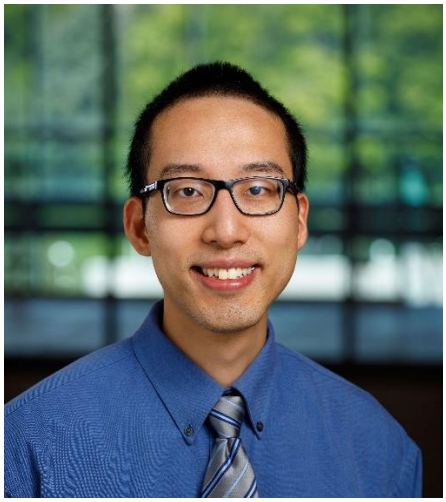
Doctoral Dissertation Defense Announcement

Group Sequential Designs and Sample Size Determination for Comparing Covariate-adjusted Survival Probabilities and Restricted Mean Survival Times



Peter Zhang

Candidate for Doctor of Philosophy

Biostatistics

School of Graduate Studies

Medical College of Wisconsin

Committee in Charge:

Michael Martens, PhD (Mentor)

Brent Logan, PhD (Mentor)

Kwang Woo Ahn, PhD

Soyoung Kim, PhD

Wael Saber, MD

Date: Thursday, May 30, 2024

Time: 9:00 AM (CST)

Defense Location: MEB 2050-2070

Zoom: https://mcw-edu.zoom.us/j/91769927802?pwd=T09adWhCZmsrQldEQzFheENVWWlndz09

Meeting ID: **917 6992 7802** Passcode: **faw62J04**

Graduate Studies:

Statistical Models and Methods I

Statistical Models and Methods II

Mathematical Statistics I

Mathematical Statistics II

Biostatistical Computing

Research Seminar

Introduction to Bayesian Analysis

Linear Models I

Theory of Survival Analysis

Introduction to Translational Bioinformatics

Design and Analysis of Clinical Trials

Biomedical Applications and Consulting

Statistical Genetics

Statistical Consulting

Introduction to Statistical and Machine Learning

Advanced Statistical Computing

Advanced Bayesian Analysis

Applied Survival Analysis

Advanced Statistics I

Reading and Research

Ethics & Integrity in Science

Research Ethics Discussion Series

Doctoral Dissertation

Dissertation

Group Sequential Designs and Sample Size Determination for Comparing Covariate-adjusted Survival Probabilities and Restricted Mean Survival Times

Group sequential (**GS**) designs are commonly employed in clinical trials with censored survival data and staggered entry, in which the survival experience is viewed sequentially and examined multiple times at interim analyses. GS clinical trials incorporate the possibility of terminating the trial early by rejecting the null hypothesis due to strong evidence of efficacy or accepting the null hypothesis for futility.

In the absence of proportional hazards, alternative metrics to the hazard ratio that can be employed to quantify the difference of two treatment groups in a time scale are the difference in survival probabilities (**SP**s) at some fixed follow-up time and the difference in restricted mean survival times (**RMST**s) limited to a specific time window. In this dissertation, we consider two statistical methods for analyzing GS designs that compare two treatment groups with time-to-event outcomes and allow for interim analyses with covariate adjustment in the presence of nonproportional hazards. The first method concerns GS procedures for comparing two survival curves at a prespecified time point, whereas the second method deals with GS clinical trials comparing two RMSTs up to a restriction time point. Both GS methods are adjusted for baseline covariates under a stratified proportional hazards regression model with stratum representing treatment group. The covariate-adjusted estimates of treatment-specific SPs and RMSTs are valid whether or not the PH assumption holds for the treatment effect. We show that the joint distributions of repeatedly computed Wald test statistics can be approximated by a canonical joint distribution with independent increments. These asymptotic distributions allow for marginal comparisons of SPs and RMSTs at multiple analyses and facilitate critical value and power calculations for maintaining a given Type I error probability. Simulations demonstrate that both methods meet targeted Type I error rate and power specifications in trials with realistic sample sizes. As an application, we illustrate the proposed covariate-adjusted GS tests using a real clinical trial dataset from the Blood and Marrow Clinical Trials Network 1101 study. In order to facilitate the usage of the covariate-adjusted GS methods studied in this dissertation, we develop an R software package that will be made publicly available for download.

Peter K. Zhang
Curriculum Vitae
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Education

M.D.	Medical College of Wisconsin	May 2026 (anticipated)
PhD, Biostatistics	Medical College of Wisconsin	May 2024 (anticipated)
Bachelor of Science in Mathematics with Honors, Computer Science, and Economics	University of Michigan	May 2018

Research Experience and Employment

Group Sequential Designs and Sample Size Determination for Comparing Covariate-adjusted Survival Probabilities and Restricted Mean Survival Times
Division of Biostatistics, Medical College of Wisconsin
PhD Candidate
Advisors: Michael Martens, PhD; Brent Logan, PhD
2020-2024

A Time Dependent Increase in Wait Times For Obtained Oncology Related Care
Collaborative for Healthcare Delivery Science, Medical College of Wisconsin
Research Assistant
Advisor: Liliana Pezzin, PhD
2021-2024

Estimation of Average Treatment Effects
Department of Economics, University of Michigan
Honors Thesis
Advisor: Linda Tesar, PhD
2017-2018

Statistics and Biostatistics Tutor
2022-2024

Honors and Awards
2024 Society of Clinical Trials Thomas C. Chalmers Student Scholarship Finalist
2023 Graduate Student Poster Award
2018 Sims Honor Scholarship in Economics
2018 Ferrando Honors Prize
2018 Phi Beta Kappa
2017 24 Month University of Michigan Hospitals Volunteer Service Award
2017 James B. Angell Scholar
2015-2018 University Honors
2014 M.S. Keeler Mathematics Scholarship
2014 Regents Merit Scholarship

Publications
Zhang, P.K., Logan, B.L., and Martens, M.J. (2024). Covariate-adjusted Group Sequential Comparisons of Survival Probabilities. arXiv. https://arxiv.org/abs/2403.17117.
Under revision.

Zhang, P.K., Logan, B.L., and Martens, M.J. (2024). Covariate-adjusted Group Sequential Comparisons of Restricted Mean Survival Times.
In progress.

Software:
Zhang, P.K., Logan, B.L., and Martens, M.J. (2024). R package "aspRMST".
In progress.

Oral Presentations:
Zhang, P.K., Logan, B.L., and Martens, M.J. Group Sequential Designs for Comparing Covariate-adjusted Survival Probabilities. Society for Clinical Trials Conference. 2024. Boston, MA

Zhang, P.K., Logan, B.L., and Martens, M.J. Group Sequential Designs for Comparing Covariate-adjusted Survival Probabilities. *Eastern North American Region (ENAR) Biostatistical Conference. 2024. Baltimore, MD*

Poster Presentations:
Zhang, P.K., Logan, B.L., and Martens, M.J. Group Sequential Designs for Comparing Covariate-adjusted Survival Probabilities. Medical College of Wisconsin Graduate Poster Session. 2023. Milwaukee, WI

Zhang, P.K., Logan, B.L., and Martens, M.J. Group Sequential Designs for Comparing Covariate-adjusted Survival Probabilities. M.D./Ph.D. National Student Conference. 2023. Copper Mountain, CO

Leadership and Community Service:

2023-2024 MCW Graduate Student Association President
2022-2023 MCW Graduate Student Association Secretary
2019-2023 MCW Orchestra Treasurer
2021-2022 MCW Graduate Student Association Biostatistics Representative
2020-2021 MCW MSTP Student Council, G1 Representative
2020-2021 MCW Step 1 Tutor
2018-2019 Greater Milwaukee Free Clinic Student Volunteer
2015-2018 University of Michigan Pre-Medical Club Treasurer
2015-2018 Michigan Finance and Mathematics Society Treasurer
2014-2018 Michigan Medicine Main Hospital Student Volunteer