Clinical Research Support Center

Shigeru Kageyama, *Professor and Director* Masako Nishikawa, *Associate Professor*

General Summary

The Clinical Research Support Center was founded in April 2014 to promote the proper conduct of clinical research. The center has the following functions: protocol planning, statistical analysis, monitoring, support for clinical research conduct, and education. We started consulting for clinical research in September 2014 and had 19 protocols of consultation. Consultations were as follows: 8 protocols for protocol planning and statistics (objective of the research, study design, control arm, randomization, primary endpoint and its rationale, procedure to avoid/reduce bias, data collection, stopping criteria, statistical analysis, analysis sets, methods of handling missing values, sample size calculations, and estimation of study duration), 1 protocol for preparing a random allocation table, and 10 protocols for conducting statistical analysis. Consultations were requested by the Departments of Anesthesiology, Diabetes, Metabolism and Endocrinology, Neurosurgery, Cardiovascular Surgery, Digestive Surgery, Clinical Oncology/Hematology, Endoscopy, and Psychiatry; the IT Strategy Office; and students of the nursing master's degree course. In cooperation with the Division of Clinical Pharmacology and Therapeutics we held a "Clinical Trial Seminar" 4 times to improve literacy about clinical trials among researchers. The themes were survival data analysis, conflicts of interest in medical research, how to prevent misconduct of clinical research, and ethical guidelines for medical and healthcare research involving human subjects.

Research Activities

Statistical methods of analyzing survival data

In the analysis of survival data, an individual is subjected to an event due to only 1 of several distinct types of causes, and the occurrence of 1 type omits other types of causes, such as death due to stroke and death due to myocardial infarction. These event types are given the statistical term "competing risks." We explored the performance and properties of the Lunn-McNeil technique, which enables the statistical inference and testing of differences in the hazard ratio between competing risks for the same risk factor in a single model formulation, with a simulation study. The performance and properties of the Lunn-McNeil technique was compared with those of a separate model, in which the Cox proportional hazards model is applied by a competing risk.

In survival data analysis, we often encounter "partly interval-censored data," for example, progression-free survival in oncology studies, in which observed data include both the exact times of events (e.g., death) and "interval-censored data" (e.g., progression). Among regression methods for partly interval-censored data, we compared the performances and properties of the R package "IntCox," which has been used for interval-censored data analysis recently in R packages, with those of the most common, but ad hoc,

method (to impute a certain value for a censoring interval (e.g., the right-point, the mid-point of the censoring interval), then applying the Cox proportional hazard model) due to the lack of an appropriate method or available software, by simulation study of 200 patients in which the design was based on actual clinical trials.

Publications

Ooba N*[1]*, Sato T*[2]*, Wakana A*[3]*, Orii T*[4]*, Kitamura M, Kokan A*[5]*, Kurata H, Shimodozono Y*[6]*, Matsui K*[7]*, Yoshida H, Yamaguchi T*[8]*, Kageyama S, Kubota K*[1] *([1]Grad Sch Med Univ Tokyo, [2]Tokyo Univ Sci, [3]MSD K.K., [4]NTT Med Ctr, [5]EliLilly Jpn, [6]Kagoshima Univ, [7]Showa Univ, [8]Tohoku Univ Grad Sch Med). A prospective stratified case-cohort study on statins and multiple adverse events in Japan. *PLoS One*. 2014; **9:** e96919.

Kadokura T*[1]*, Akiyama N*[1]*, Kashiwagi A*[2]*, Utsuno A*[1]*, Kazuta K*[1]*, Yoshida S*[1]*, Nagase I, Smulders R*[3]*, Kageyama S ([1]Astellas Pharma Inc., [2]Shiga Univ Med Sci, [3]Astellas Pharma Global Dev Eur). Pharmacokinetic and pharmacodynamic study of ipragliflozin in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled study. *Diabetes Res Clin Pract*. 2014; **106:** 50-6.

Reviews and Books

Kageyama S. Investigator-initiated clinical trials score and quality assurance (in Japanese). *Iyaku Janaru*. 2015; **51:** 51-5.