Statistical Issues in the Analysis of Neurological Studies

A Harvard Catalyst Biostatistics Symposium

November 19, 2014
11:00am - 4:00pm
Shriners Auditorium, MGH
11:00am | Welcome and Opening Remarks
Rebecca Betensky, PhD
Professor of Biostatistics, Harvard School of Public Health
Program Director, Harvard Catalyst Biostatistics and Bioinformatics Program

11:05am | Clinical Viewpoint: Examples of Analytical Issues in Neurological Diseases
James Berry, MD, PhD
Assistant Professor of Neurology, Massachusetts General Hospital

ALS is a neurodegenerative disease with only one FDA-approved disease modifying therapy, riluzole. The beneficial effect of riluzole is modest, and there is urgent need for novel therapy development. Therapy development is hampered by the lack of a very clear initiating pathophysiology in most cases, and by the rapidity of disease progression and relative rarity of the disease. There is tremendous pressure to develop therapies quickly, yet avoid the costly mistake of transitioning therapies to Phase III trials only to see negative results. Thus, the design of Phase II trials is a critical stage of drug development both for novel therapies and for those that are being repurposed from another indication. One substantial issue in ALS trial design has been that early phase (small, short duration) ALS trials have used the same efficacy outcome measures as larger Phase III trials. These Phase II trials are often pre-destined to miss statistical significance and yield difficult-to-interpret results. Thus, we are searching for better methods, which might include larger Phase II trials, more sensitive outcome measures, pharmacodynamic markers, or a shift to the search for “transformative therapies.” All of these have both theoretical benefits and logistical drawbacks.

12:00pm | Lunch

1:00pm | Causal Inference in Neurological Studies

2:00pm | Multiple Endpoints in Neurological Studies

2:45pm | Break

3:00pm | Measurement Issues in Short Term Clinical Trials

Statistical Issues in Alzheimer’s Disease
Deborah Blacker, MD, ScD
Professor of Psychiatry, Massachusetts General Hospital

This talk will provide an overview of key challenges in analyzing data about Alzheimer’s disease, a late onset, highly prevalent disorder with a long prodrome and frequent mixed underlying pathology. These and other factors lead to measurement uncertainty for both diagnostic categories and longitudinal measures, multiple partly correlated and complexly sequenced potential biomarkers and clinical measures with (generally) sigmoid distribu-
Statistical Issues in Multiple Sclerosis
Tanuja Chitnis, MD
Clinical Affiliate in Neurology, Brigham and Women’s Hospital

Multiple sclerosis has many unanswered questions. Among these are: 1) risk factors including genetic predictors of MS disease versus health; 2) predictors of conversion from a monophasic form of MS to a chronic disease; 3) predictors and correlates of disability accumulation; 4) predictors of response to specific treatments. The numerous challenges lie in identifying the appropriate predictors as well as outcome measures for any of these questions. As well, accounting for multiple factors that contribute to outcomes in this multifactorial disease is important. A number of the major outcome measures recorded in the clinical setting are subject the physician subjectivity which needs to be accounted for in the analysis.

Slowing Progression of Parkinson’s Disease: How do you Measure That?
Michael Schwarzschild, MD, PhD
Professor of Neurology, Massachusetts General Hospital

The core neurological symptoms of Parkinson’s disease (PD), in contrast to those of most other neurodegenerative diseases, can be treated effectively even if only partially by dopamine-replacement therapies. However no treatment has been established to slow progression of the disease. A major challenge in the design of clinical trials of candidate neuroprotectants for PD is selection of the outcome measures and statistical analyses that will most meaningfully answer, ‘Does the treatment slow progression of PD?’ The seemingly simplest analysis of a difference between active and placebo arms for the rate of worsening by a standard clinical scale (e.g., the Unified Parkinson’s Disease Rating Scale [UPDRS]) is generally confounded by those symptomatic benefits of standard dopamine-replacement therapies. Although there remains no clear regulatory, scientific or clinical standard for the design of disease-modification trials in PD, multiple novel outcomes and analysis strategies are being pursued and will be discussed.

12:00pm | Lunch

1:00pm | Causal Inference in Neurological Studies

Introduction
David Schoenfeld, PhD
Professor of Medicine, Massachusetts General Hospital

Analyzing Supportive Care in ALS
Erin McDonnell, MS
Biostatistician, Massachusetts General Hospital

Many amyotrophic lateral sclerosis (ALS) patients rely on forms of palliative care such as gastric tube and non-invasive ventilation (NIV) to assist with everyday tasks throughout disease progression. Effects of these treatments on survival have been explored, although biased results may have stemmed from confounding by indication in observational studies. The objective of this talk is to discuss the recent application of two causal inference methods to ALS supportive care research. In 2011, Atassi, Cudkowicz, and Schoenfeld fit marginal structural models in order to obtain unbiased effect estimates of supportive care on survival amidst time-dependent confounding from forced vital capacity and the revised ALS functional rating scale. They found that NIV had no effect on survival while feeding tube placement led to a 0.28 increase in the hazard of death (p=0.02). To complement their work, we fit structural nested accelerated failure time models to observational data on 392 participants in a recent ALS clinical trial. Findings indicate that NIV increased patients’ survival time by 49% (p = 0.03) while feeding tube placement decreased patients’ survival time by 39% (p = 0.03). These two causal inference analyses demonstrate the need for proper statistical techniques in the face of confounding by indication in observational data. In conclusion, NIV may be of benefit while gastric tube placement may lead to shortened survival. We consider possible clinical explanations for this harmful effect of gastric tube placement, including stress or complications during the gastric tube placement procedure.

Use of Observational Data to Make Causal Inferences About Treatment Decisions in Multiple Sclerosis
Brian Healy, PhD
Assistant Professor of Neurology, Brigham and Women’s Hospital

In the past 20 years, many treatments have been approved by the FDA for the treatment of multiple sclerosis. Each of these treatments has demonstrated efficacy by reducing the relapse rate compared to placebo, and some head-to-head treatment comparisons have been completed. At the same time, many treatment comparisons and clinical questions related to treatment decisions have not been addressed in randomized clinical trials. Given the many potential treatment regimens that patients can follow, clinicians must make treatment decisions with little or no information to guide the treatment decision.
In the last 10 years, several authors have begun to investigate clinical questions using observational data with appropriate statistical analyses to control for confounding. These approaches have addressed several questions about how to treat MS patients including the long-term effect of interferon and whether patients with a relapse should change treatment. Over the next five years, the use of these techniques will grow as the number of clinical questions that can only be addressed using observational data increases.

Adjustment for Selection Bias and Mediation Analysis in Neuropathological Studies of Alzheimer’s Disease

Jing Qian, PhD
Assistant Professor of Biostatistics, University of Massachusetts, Amherst

Using the autopsy cohort of National Alzheimer’s Coordinating Center (NACC) dataset derived from the Alzheimer Research Centers, the largest neuropathological database existing, we recently assessed the impact of the Alzheimer’s disease (AD) pathologic process on AD-associated cognitive decline, and examined the clinical and pathological consequences of inheriting the risk allele APOE ε4 and the protective allele APOE ε2. A potential concern of autopsy studies is that their conclusions may not be generalizable to the subjects who died but did not undergo autopsy, because the decision to consent for autopsy may be associated with bias. In this talk, we will discuss how to adjust for selection bias due to autopsy using the inverse probability weighting technique. It is also of interest to assess whether there is a direct effect of APOE alleles on cognition and/or an indirect effect through common AD pathological hallmarks. We will describe how to estimate the direct and indirect effects of APOE alleles through causal mediation analysis.

2:00pm | Multiple Endpoints in Neurological Studies

Introduction
Eric Macklin, PhD
Instructor of Medicine, Massachusetts General Hospital

Combining Endpoints Using a Global Rank Test
Ritesh Ramchandani
PhD Student, Department of Biostatistics, Harvard School of Public Health

In clinical studies, a single outcome does not always adequately capture the effect of an intervention, so other outcomes are often considered as well. In ALS studies, for example, mortality and decline in neurological function are often considered co-primary endpoints. We describe a general nonparametric scoring method for combining two or more endpoints into a single summary statistic that measures efficacy. First we score each pair of subjects with respect to each outcome, and then reduce the dimension of the multiple pairwise scores to get a composite score for the pair of subjects. A rank-sum type test on the composite scores is then performed. The method of dimension reduction is investigator chosen, and examples of the different possible tests are provided. We also propose methods for choosing optimal outcome weights to improve the power of certain tests under specific alternative hypotheses. The tests are illustrated on an ALS dataset.

Power and Sample Size Calculations for the Wilcoxon–Mann–Whitney Test in the Presence of Missing Observations due to Death
Rebecca Betensky, PhD
Professor of Biostatistics, Harvard School of Public Health
Program Director, Harvard Catalyst Biostatistics and Bioinformatics Program

We consider a clinical trial of a potentially lethal disease in which patients are randomly assigned to two treatment groups and are followed for a fixed period of time; a continuous endpoint is measured at the end of follow-up. For some patients, however, death (or severe disease progression) may preclude measurement of the endpoint. A statistical analysis that includes only patients with endpoint measurements may be biased. An alternative analysis includes all randomized patients, with rank scores assigned to the patients who are available for the endpoint measurement based on the magnitude of their responses and with “worst-rank” scores assigned to those patients whose death precluded the measurement of the continuous endpoint. We consider different approaches for assigning the worst-rank scores and derive sample size and power formulas that recognize the problem of early death.

2:45pm | Break

3:00pm | Measurement Issues in Short Term Clinical Trials

Introduction
Brian Healy, PhD
Assistant Professor of Neurology, Brigham and Women’s Hospital

Measurement Issues in Short Term Clinical Trials of Multiple Sclerosis
Brian Healy, PhD
Assistant Professor of Neurology, Brigham and Women’s Hospital

Multiple sclerosis (MS) is the most common neurologic disease among young people in the US. The majority of MS patients initially have a relapsing-remitting form of the disease, and most of the available treatments have been approved by the FDA by demonstrating an effect in terms of reducing the number of relapses. At the same time,
the more devastating part of the disease is neurodegeneration, and the impact of the available treatments on neurodegeneration, especially over the long term, is uncertain. In fact, recent observational analyses have questioned whether treatments have an impact on long term neurodegeneration. One of the problems with estimating the treatment effect on the neurodegenerative component of the disease is related to challenges in reliably measuring neurodegeneration, especially in the short term. The primary clinical outcome measure in most clinical trials is the presence of sustained progression on the EDSS. Using data from the Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women’s Hospital (CLIMB), problems with the definition of sustained progression were observed when longer term follow-up was considered. Whole brain atrophy or gray matter atrophy have been proposed as alternative measures of neurodegeneration, but these measures have not been validated for use as the primary endpoint in a phase III clinical trial. Novel measures and approach for analysis are required to accurately assess treatment effects on the development of neurodegeneration.

Measurement Issues in Parkinson’s Disease
Eric Macklin, PhD
Instructor of Medicine, Massachusetts General Hospital

Estimating effects of treatment in Parkinson disease (PD) is complicated by difficulty separating symptomatic from disease modifying effects of new interventions and by variable but substantial effects of existing approved drugs. These issues are addressed by choice of study design, selection of outcome measures, and elements of statistical analysis. I present the planned phase 3 trial of urate as an example and identify some alternative approaches used in other trials.

3:30pm | General Discussion

About Harvard Catalyst Biostatistics:
The Harvard Catalyst Biostatistics Program supports Harvard clinical and translational investigators. Drawing on a team of highly skilled biostatisticians from the Harvard academic and hospital community, the program offers consultations on a range of topics as well as software tools to researchers as they design new studies. The program also provides training for clinical investigators in the principles and methods of biostatistics via the Harvard Catalyst Introduction to Clinical Investigation course; and seminars, lectures, and workshops. In addition, the program promotes the intellectual and professional development of Harvard Catalyst biostatisticians.
For more information about the Harvard Catalyst Biostatistics Program, please visit: http://catalyst.harvard.edu/programs/biostatistics/

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