PERSPECTIVES ON OBSERVATIONAL ANALYSES OF MEDICATION USE IN WHI COHORTS

Ross Prentice, and the WHI Medication Analysis Group (9/24/11)

1. Background

The WHI, with its well-characterized cohorts and periodic medication (and supplements) inventory, has potential to provide useful information on medication effects on clinical outcomes. However, since decision-making concerning medication use can involve 'indicators' that are related to some clinical outcomes, such observational analyses can be challenging indeed.

To illustrate such challenges consider postmenopausal hormone therapy (HT, both estrogen-alone and estrogen plus progestin), which has been studied in the WHI Clinical Trial and Observational Study. The WHI has excellent data on HT use involving a baseline interview, and update (at least annual) of adherence to assigned treatment (CT) or changes in medication use (OS). In spite of the quality of the HT use history, there were some noteworthy differences between CT and OS findings after applying standard confounding factor procedures in the OS data analysis. More specifically, a reasonable agreement between CT and OS results could be achieved for some key clinical outcomes (coronary heart disease, breast cancer) only after allowing for certain timing issues (time from menopause to first use of HT, time since HT initiation) as well as outcome-specific confounding variables (e.g., Prentice et al, AJE, 2009;170:12-23). For other outcomes, including stroke, hip fractures, and total mortality, these analytic maneuvers were insufficient. To cite but one example, the estimated E+P hazard ratio for hip fracture was

3.10 times higher (95% CI: 1.20, 7.98), and in the opposite direction from the null, in the OS versus the CT. While the reasons for this discrepancy are not clear, it seems likely that many OS women initiated E+P at least in part because of bone density concerns. If so, time-dependent data on both E+P use and on concerns about osteopenia/osteoporosis/fractures would need to be available across the follow-up period to have the opportunity to control for this source of 'confounding by indication' in the OS.

The quality of observational medication analyses in WHI will depend crucially on the availability of the necessary confounding control data, and on the availability of data to construct the medication use history over time. Without these essential building blocks the estimated associations will not be interpretable, regardless of the analytic method used.

2. Data Analysis Options

Most WHI medication analyses will involve time-to-event outcomes. Let h{t; Z(t), X(t)} denote the hazard rate for a time-to-event outcome at time t following WHI enrollment, for a woman having history of the study medication prior to time t of Z(t), and confounding factor history prior to time t of X(t). For a simple binary treatment one can write

Z(t) = {z(u), u < t} where z(u) = 1 if the woman is using the treatment at following time u and z(u) = 0 otherwise.

For X to confound the association between Z and the clinical outcome, h{t, Z(t), X(t)} must depend on X(t), and also the medication use probability

p{z(t) = 1|X(t)} must depend on X(t). Conceptually, the confounding by X can be avoided through modeling and accommodation of the dependence on X in either of these two functions.

A classical approach to confounding control may use a Cox model

$$h\{t, Z(t), X(t)\} = h_0(t) \exp\{\beta_1^T z(t) + \beta_2^T x(t)\} \qquad (1)$$

where x(t) is a fixed length vector formed from X(t). [Note that the 'baseline' hazard rate h_0 can also be stratified in a time-dependent fashion based on X(t).] This method works well in many situations, even if treatment decisions depend on X(t).

A closely related approach to confounding control involves fitting a model, for example a logistic regression model, to

$$p\{z(t) = 1|X(t)\}$$

The corresponding estimated treatment probabilities (at follow-up time t) are sometimes referred to as propensities (Rosenbaum and Rubin, Biometrika 1983;70:41-55). These propensities may be used as components of x(t) in the hazard rate model (1) for confounding control.

Association studies of medication use are particularly challenging if a time-dependent covariate x(t) influences the treatment choice z(t), which in turn affects subsequent values of x (i.e., x(u), u > t) since the history X(t) can then be both confounder and mediator of treatment effect. Robins et al (Epidemiology 2000;11:550-560) assert that their so-called marginal structural models can address this type of situation. A marginal structural modeling approach introduces inverse-probability-of-treatment weights into the association parameter estimation procedure. For example, in the Cox model (partial) likelihood estimating function, the contribution of an individual (at

risk at follow-up time t) under treatment is weighted inversely by the propensity score mentioned above and the contribution of an individual not under treatment is weighted inversely by one minus this propensity score. There are also some refinements related to reducing the variability in these weights. We have used related methods in WHI, for example, for adherence-adjusted analyses in CT.

Careful consideration will need to be given in each application to the adequacy of WHI data for constructing the histories {Z(t), X(t)}. This is especially true in the OS for Z(t), since medication use data is then typically available only at baseline and Year 3.

3. Issues to be Considered in the Analysis of WHI Observational Medication Data

Medication Use History { Z(t), t>0}:

The data analyst and manuscript writing group will need to consider whether WHI has data that allow a reliable approximation to each participant's medication use history to be constructed. Since medication inventories were obtained only at baseline, and years 1, 3, 6 and 9 in the CT, and only at baseline and year 3 in the OS, there may be limited ability to study medications having marked changes usage patterns during WHI follow-up, or medications that tend to involve short usage episodes that may be missed by a snapshot as infrequently as every three years. A closely related consideration, especially in the OS, is the time period relative to WHI enrollment for which the WHI data are viewed as sufficient. For example, an analysis could choose to censor the follow-up for a woman three years after her most recent medication data collection (e.g. 6 years from enrollment for most OS women, 12 years from enrollment for some CT

women) to avoid the use of medication data that are too out-of-date. There is also the possibility of more complex data analyses that would use covariate measurement error methods for dealing with the incompleteness of the medication data. For example the availability of 6 and 9 year medication data in the CT may support the use of longer-term outcome data in the OS by imputing 'regression calibrated' medication use data at years 6 and 9 in the OS. These methods may require some specialized software.

Confounding variable history {X(t), t>0}:

The ability to be convincing concerning confounding control in analyses of this type represents a major challenge. If decision making concerning the use of a specific medication is thought to be unrelated to the clinical outcome under study it may be sufficient to apply standard confounding control methods. The reliability of the result will depend on the completeness of the set of potential confounding factors entertained, and the fact that WHI cohorts are well characterized in terms of standard risk factors for several major clinical outcomes, is a major advantage. The data analyst can consider whether some updating of potential confounding factor data over the study follow-up period would be helpful.

On the other hand, if decision making concerning medication use depends on perceived risk for the clinical outcome under study one needs to be able to argue that data X(t) that are sufficient to characterize the participants risk are available, at each follow-up time t. If so, then conditioning on X(t) should allow a ' fair' assessment of risk in relation to variation in the corresponding modeled z(t). Note that variation in z(t) may include dosage and aspects of the medication schedule that may also reflect perceived

risk for the study outcome, in which case X(t) needs to include data sufficient to characterize this aspect of perceived risk will also be needed. It will be a judgment matter in any particular application as to whether confounding factor data are sufficiently comprehensive and timely to support a useful interpretation for related medication association with study outcomes. The linkage of WHI cohort data with CMS data may be helpful for this purpose, since this source may provide additional and more frequent information data on both use of the medication under study as well as on other medications that may help to characterize decision making concerning the use of such medications and the related dose and schedule.

A further complication may arise in this complex setting where confounding factor data may inform decision making concerning medication use, if the medication affects later values of the confounding factor data. In this situation control for X in a hazard ratio regression analysis may over-adjust if the confounding factor in question also mediates some or all of any association between the medication and clinical outcome under study. This possibility should be considered in interpreting medication association analyses in WHI. Also, some further evaluation of the claim that marginal structural models can accommodate factors that both confound and mediate would be worthwhile.

4. Summary

In summary, the potential for observational medication association analyses depends crucially on the ability to construct pertinent medication use histories Z(t) over the study follow-up period, and on the ability to define and construct needed confounding variable histories X(t) over the study follow-up period. There are also choices related to the

specification of regression variables z(t) and x(t) in (1); for example, duration of medication use by time t may be an important element of z(t). Data limitations will be the most important issues for most such analyses, and the ability to posit a 'causal' interpretation to an association analysis will depend primarily on the extent and quality of the { Z(t), X(t)} data. Data analytic choices will also play a role, with either classical confounding factor methods or more recent marginal structural model methods expected to be suited to most such analyses if the data are adequate. The latter (marginal structural) approach may offer some advantages if there are complex interrelations over time between treatment decisions and confounding/mediating factors, and it will be desirable for WHI to gain experience in the use of these methods in the context of observational association studies of medication use.