**Chapter 15**

**Matched Case Control Studies**

with Arthur Williams, PhD, and Etienne Pracht, PhD

# [H1] Learning Objectives

**[INSERT NL]**

1. Identify data in electronic health records that can be used to evaluate the comparative effectiveness of different interventions

2. Define a case that has received an intervention and matched controls who have not received an intervention

3. Contrast outcomes for cases that have received an intervention to matched controls

4. Test if the difference of cases and matched controls is statistically significant

5. Visually display data for outcomes of cases and matched controls over time

6. Discuss the variables that can be used to match controls to intervention cases

**[END NL]**

# [H1] Key Concepts

**[INSERT BL]**

* Cases
* Matched controls
* Observation period
* Enrollment event
* Follow-up period
* Exposure to treatment
* Time to event
* Verification of matching
* Overlap in matching
* Confidence interval

**[END BL]**

# [H1] Chapter at a Glance

Managers often need to compare the effectiveness of different interventions. One method of doing so is employing matched case controls. This approach can be put to a variety of uses, including evaluating the impact of a program, the productivity of employees, or the market penetration of varying initiatives. Cases are selected from those who have received an intervention; controls are selected from those who have not. Cases are matched to controls based on a set of characteristics (covariates). Once matched, the difference in outcome of cases and controls is reported. This chapter describes a nested, matched, case/control design using retrospective data inside electronic health records (EHRs). It defines the enrollment, observation, and follow-up periods, as well as how cases and controls are matched. Finally, the chapter describes statistical procedures for verifying that matching was done correctly and that the intervention was statistically significant.

# [H1] Widespread Application

Managers are often called on to make judgments of the comparative effectiveness of various interventions. The following sections describe some examples.

**[H2] Marketing Decisions**

In marketing, cases and matched controls are needed to examine the effectiveness of competing marketing initiatives. For example, Hollon and colleagues (2003) used this technique to evaluate the effectiveness of direct-to-consumer marketing efforts.

**[H2] Strategic Planning**

In strategic planning, this method can be used to assess the likelihood of success of different plans. For example, Mattes and colleagues (2006) used this method to evaluate the likelihood of commercial success of new inventions.

**[H2] Quality Control and Process Improvement**

Case control studies are often used to assess quality of care. As an analyst evaluates changes in a clinical process, cases represent patient experience after a change is made and matched controls represent patients who were treated before the change was instituted. For example, Sundberg and colleagues (2014) contrasted the cost and effectiveness of integrated pain management. They identified pain patients who had received integrated management and contrasted them to pain patients who had received conventional care but had the same pain diagnosis, age, gender, and sociodemographic factors. Others have used matched case control approaches to study quality factors that lead to unplanned readmissions (Scott, Shohag, and Ahmed 2014). Danielsen and Rosenberg (2014) showed that patient education could reduce the cost of care. Grammatico-Guillon and colleagues (2014) used matched case control to monitor a hospital discharge database for hip and knee arthroplasty-related infections. Anantha and colleagues (2015) used matched case controls to examine the cost and timing of care (day or night) for emergency general surgery. Dykes and colleagues (2012) used matched case controls to assess measures to improve patient safety.

One must recognize, however, that conclusions drawn from such studies must be used with care because two or more groups of patients are compared. Study success depends heavily on the degree to which matching removes unwanted or outcome-irrelevant variations in patient characteristics, while the likelihood of successful application in practice can depend on whether the study groups possess characteristics similar to those of others to which the intervention will be applied in the future.

**[H2] Health Information System Evaluation**

Case control approaches can be used to evaluate the effectiveness of EHR systems. For example, the relationship between computerized provider order entry and pediatric adverse drug events can be assessed (Yu et al. 2009), as can the effectiveness of care received remotely via telemedicine compared with that received in a typical hospital or physician office setting (Palen et al. 2012). Matched case controls have also been used to evaluate public health and occupational health programs (Cullen, Checkoway, and Alexander 1996).

**[H2] Finance and Cost-Effectiveness**

The use of case control studies to conduct cost-effectiveness analysis is common (Vonkeman et al. 2008). A retrospective matched case-control study was conducted to assess the financial impact of treating pediatric ventilator-associated pneumonia. The analysis provided the first demonstration of significant, sustained reductions in rates following the implementation of a costly prevention bundle (Brilli et al. 2008). Others have used this method to examine the profitability of business operations (Bijl, Kooistra, and Hogeveen 2007), to examine hospital closure (Longo and Chase 1984), to examine the cost-effectiveness of robotic surgery (Sarlos et al. 2010), and to examine expenditures before and after surgical interventions (Relph et al. 2013).

**[H2] Predictive Medicine**

A novel application was made in predictive medicine using the matched cases and controls. Data from EHRs were used to select cases from Geisinger Health System primary care patients with a diagnosis of heart failure. Controls were randomly selected, then matched with cases based on sex, age, and the clinic providing care. The study demonstrated that it was possible to predict heart failure six months before a clinical diagnosis was made.

**[H2] Human Resource Decisions**

The US Army used the matched case control method to assess risk factors for disability retirement among its personnel (Niebuhr et al. 2011). Matched case controls have also been used to evaluate the effectiveness of pre-employment screening (Sorgdrager, Hulshof, and van Dijk 2004).

Matched case control studies have been broadly applied, and the approach has a long history of application in epidemiology and medical statistics. Use of matched case control studies in the analysis of data from EHRs is now quite common, and considerable advances in theory, methods, and practice of case control designs continue to be made in epidemiology and biostatistics.

# [H1] Study Design and Methods

Many different techniques have been developed to conduct comparative effectiveness studies (Institute of Medicine 2013). A frequent complaint is that different comparative effectiveness methods or approaches can lead to contradictory conclusions (Lohr 2010). Contradictions can occur because conclusions are based on nonrandomized data and observations drawn from a wide variety of disparate sources and patients, including databases used for insurance claims, prescription histories, national registries, and patient treatment records. Lacking true random sampling, studies must be carefully designed to ensure that data are representative of a larger population with the characteristics and outcomes being assessed. This chapter describes procedures for conducting a retrospective matched case control study of comparative effectiveness.

# [H1] Definition of Cases and Controls

Patients who receive an intervention are referred to as *cases*. Patients who do not receive an intervention are referred to as *controls*. For example, patients who were admitted to the Department of Veterans Affairs’ (VA) medical foster home (MFH) program may be considered cases, and patients in traditional nursing homes may be considered controls. MFHs allow patients to rent a room in an approved residence in a community and receive home-based medical and social services from the VA. In the nursing home option, patients live with a number of other residents in an institutional setting in which their food, social, and other activities are organized for the entire group. In VA nursing homes, medical care is colocated in the same facility and therefore can be delivered conveniently and quickly. In the MFH, medical care is delivered to the veteran through home health care, other modalities, or removal to a hospital or clinic for treatment.

In this and other settings, the identification of cases among medical records can be difficult, as administrative databases typically record utilization of services, not necessarily participation in a program or a need for care. There are at least two methods for identifying a case, the first of which is examining the medical record for a unique clinical event of interest. A clinical event can be a physician office visit, inpatient admission, or emergency department (ED) visit. For a study of heart failure, for example, a clinical event could be an initial diagnosis of congestive heart failure. Typically, these events are defined using codified nomenclature such as the International Classification of Diseases (ICD).

The Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality has defined how various diagnoses codes correspond to common disease categories. For example, heart failure can have one of two dozen ICD-9 codes. Other examples include falls,[[1]](#endnote-1) injuries,[[2]](#endnote-2) medication errors,[[3]](#endnote-3) mood and anxiety problems,[[4]](#endnote-4) and hospitalization encounters.

Second, a case can be identified by examining admission to a program. For example, in the MFH project, the program administrator maintains a list of patients for whom an MFH provided care.

# [H1] Measurement of Exposure to Treatment

In defining cases and controls, consideration needs to be given to the degree of exposure to an intervention. The length of exposure should be long enough that a change in outcome can be expected. For example, the day after enrollment in MFH care, no change in patient outcome is expected. It is common to assume that at least three months are needed before a patient begins to show the benefit of a change in the delivery of healthcare. This implies that patients with short stays in an MFH or in nursing homes cannot be easily evaluated for changes in the effects of service modalities on care outcomes.

Some patients can receive both the intervention and the control programs. For example, a patient may enroll in an MFH at first, but after months of enrollment leave it for a nursing home. Therefore, the time of a patient’s enrollment in a case or control group often needs to be done for specific periods or lengths. Because the same patient has spent time in both groups, he may appear to be an ideal match for himself in evaluations of the two interventions. An important exception exists—the case and its control are examined at different points in time, and this needs to be considered in the design of studies when improvements in treatment over time can affect measured study outcomes.

Unfortunately, the transition from one intervention to another is almost always accompanied by a major crisis that affects the patient’s health. Though it is the same study patient, she has a different health status after the transition. For example, in exhibit 15.1, we see information on the blood pressure of one patient. This patient was in a nursing home for seven years. At the end of the seventh year, there was a hospitalization (shown as a circle). Following this hospitalization, the patient was discharged to an MFH. The blood pressure values during year 8 show the patient’s condition in the MFH. The patient’s condition improved right before the transfer to the MFH program. The improvement may result from hospitalization not the MFH. When patients are classified into cases or controls over different periods, analytical methods for assessing treatment effects become statistically and conceptually complex. Analysts must explicitly consider *person-time* (i.e., the amount of time each patient spends as a case or a control).

**[INSERT EXHIBIT]**

**Exhibit 15.1** Patient Transitions Among Care Venues



**[END EXHIBIT]**

# [H1] Enrollment and Observation Period

The statistician should choose an enrollment period that allows selection of a large group of patients. On the left side of exhibit 15.2, patients arrive at different times during the enrollment period. Each patient is followed for a time and their outcomes noted. The period is defined relative to the enrollment event. The left side of the exhibit shows data based on the date of visits. The right side shows the same data based on time since first visit, demonstrating that patients are followed for different intervals until the outcome of interest occurs.

**[INSERT EXHIBIT]**

**Exhibit 15.2** Enrollment on Specific Dates

*Note*: Numbers in the graph show patient IDs. The letter O indicates timing of measurement of outcome.

**[END EXHIBIT]**

The observation period is typically set to one year prior to the enrollment event. During this period, no difference between cases and controls is expected. In fact, by design, controls are matched to cases so that there are no significant differences between cases and controls prior to enrollment.

As an example, consider the data in exhibit 15.3. Dates of various events are given, as well as the calculated time since enrollment in the program. Suppose the enrollment event is any diabetes-related visit after January 1; the follow-up period is one year after enrollment. The patient depicted in exhibit 15.3 visits the physician on January 9. This is the first diabetes-related visit during the enrollment period, so this becomes the enrollment event. Over the next 13 months, the patient has several encounters with his physician, as well as two ED visits. On both occasions, the ED visits were the results of falls. The time since enrollment in the study is the number of days between these fall events and the enrollment date. As exhibit 15.3 shows, one of these falls was within one year of enrollment (and therefore during the follow-up period). When data from EHRs is analyzed, it is important to specify the enrollment event, the follow-up period, and the observation period, as these time intervals identify data points used in the statistical analysis.

**[INSERT EXHIBIT]**

**Exhibit 15.3** One Sample Patient and His Encounters



# [END EXHIBIT]

# [H1] Matching Criteria

Controls can differ from cases in distinct ways. For example, controls may be older or have different comorbidities—differences that could change treatment or intervention outcomes. Consequently, it is important to match controls to cases to ensure that such differences are not attributed to the intervention or treatment. The variables used to match controls to cases differ from study to study, but often involve one or more of the following:

**[INSERT BL]**

* Observation period(when this is not done, the differences in case and controls could result from changes that have occurred over time in the environment or from the clinician’s learning process)
* Age on admission
* Gender
* Comorbidities

**[END BL]**

Another way of controlling for differences prior to enrollment is to choose controls so that they match cases in outcomes observed in the period prior to enrollment. In this fashion, cases and controls have the same history. The variables typically used in this fashion include history of hospitalization, medical errors, falls, and use of mental health services. Matching by history, however, can be difficult when all relevant medical conditions data are not in the EHR and cannot be easily found in other sources.

For a continuous variable, a control can be said to roughly (coarsely) match the case if controls are within one, or a portion of one, standard deviation. For example, if age is considered a continuous variable with a standard deviation of 1.2 years, then all controls between will match to cases who are 62 years old. For discrete variables, the case and control match exactly if they both have the same value. A coarse match may expand these definitions to neighboring values. A coarse match to age 62 may select controls plus or minus one year, from 61 to 63 years old. In matched case control studies, the study is often done first with coarse matches, then the sensitivity of findings are reexamined in tighter and less-coarse matches.

Prudence dictates that selection of standard deviation values for matches should be done while aware of the anticipated effects of controls on statistical analyses and outcomes. On occasion, helpful information can be found in the literature. For example, excluding or including potential matches because of unrealistically small or large standard deviation measures of controls is not helpful in the exercise of statistical control—the purpose of matching. In addition, standard deviation values of a size that excludes an excessive number of potential matches should not be selected.

For each case, three matching controls may be selected. Research shows that the statistical power is not improved beyond a ratio of three controls to each case (Schlesselman 1982). If more than three controls are available, the decision on which three should be selected can be done randomly. Exhibit 15.4 shows an example of how matching occurs—data for two cases who received an intervention and seven potential controls who did not. These patients are to be matched based on age, identifying as potential controls within one standard deviation. Control patients whose age is within one standard deviation for each case patient are eligible; selection of specific control patients is accomplished by choosing those with the lowest random number.

**[INSERT EXHIBIT]**

**Exhibit 15.4** An Example of Matching Controls to Cases

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Patient ID** | **Received Intervention** | **Age** | **Months to Fall** | **Random Number Between 0 and 1** | **Case or Control?** |
| **Observation Period** | **Follow-up Period** |
| 1 | Yes | 65 |  | 3 | 0.24 | Case |
| 2 | No | 60 |  | 2 | 0.85 |  |
| 3 | Yes | 84 | 2 |  | 0.64 | Case |
| 4 | No | 82 | 4 |  | 0.7 | Control |
| 5 | No | 78 |  |  | 0.87 |  |
| 6 | No | 80 | 3 |  | 0.72 | Control |
| 7 | No | 79 |  |  | 0.86 |  |
| 8 | No | 64 |  |  | 0.16 | Control |
| 9 | No | 70 |  | 2 | 0.17 | Control |
|  |
| Standard Deviation | 8.89 |  |

 **[END EXHIBIT]**

 Suppose we need to randomly select two controls for each case. For case 1, we choose patients 8 and 9. For case 2, we choose patients 4 and 6. Let’s look at the calculations for this example step by step.

**[H2] Step 1**

Calculate the standard deviation for age across all nine patients. The average age in exhibit 15.4 is 73.6 years. The standard deviation, *s*, can be calculated using the formula

**[INSERT EQUATION]**

.

**[END EQUATION]**

 In this equation, is the *i*th observation from *n* observations, and is the average of the observations. Given our data, the math works out to
**[INSERT EQUATION]**

.

**[END EQUATION]**

 **[H2] Step 2**

For each patient that received the intervention, calculate a one-standard-deviation interval based on age (see exhibit 15.5).

**[INSERT EXHIBIT]**

**Exhibit 15.5** Sample Calculations of Matching Controls to Age of Cases

|  |  |  |  |
| --- | --- | --- | --- |
| Case Patients | Control Case Age | Age – One Standard Deviation | Age + One Standard Deviation |
| Patient 1 | 65 | 65 – 8.89 = 56.1 | 65 + 8.89 = 73.9 |
| Patient 3 | 84 | 84 – 8.89 = 75.1 | 84 + 8.89 = 92.9 |

**[END EXHIBIT]**

**[H2] Step 3**

Identify eligible controls that fall within one standard deviation of the age of the case. Select two with the lowest random numbers from the eligible controls for each case.

**[INSERT BL]**

* Patient 1 is the first case patient, with an age of 65. Patients 2, 8, and 9 fall within one standard deviation of this age. Patients 8 and 9 have the lowest random numbers and can be selected as controls.
* Patient 3 is the second case patient, with an age of 84. Patients 4, 5, 6, and 7 fall within one standard deviation of this age. Patients 4 and 6 have the lowest random numbers and can be selected as controls.

**[END BL]**

These selections provide us with assignments of controls to cases matched on age. Other variables could also be used for matching, and the decision of choosing those that should be used is crucial.

 One common method for sidestepping the selection of variables for matching is to rely on a single variable, the outcome, but now measured prior to enrollment in treatment. In this fashion, cases are matched to the control on history of the prior outcome.

# [H1] Measurement of Outcomes

Outcomes are typically defined over a range of values over time. Patients may be in and out of a therapeutic range on several days. Consequently, it is important to calculate an actual time or percentage of time patients are within a therapeutic range. Rosendaal and colleagues (1993) proposed such a procedure. Exhibit 15.6 shows an example of a patient going in and out of a range for blood pressure—times when systolic blood pressures are within 120 mmHG to 140 mmHG are indicated.

**[INSERT EXHIBIT]**

**Exhibit 15.6** Examples of Blood Pressures in and out of a Therapeutic Range

 **[END EXHIBIT]**

 For two consecutive values that are in the range, the calculation is straightforward. When one value is in the range and the next is not, a linear extrapolation is made to determine the day the patient moved out of range. A preset maximum (e.g., 60 days) is used to reduce the influence of the linear extrapolation for two values that are very far apart. The percentage of days the patient is in the therapeutic range is calculated as the sum of all estimated days in the range divided by the number of days from first to last measure. For two values at two consecutive measurements, the extrapolation is based on the formula

**[INSERT EQUATION]**

.

**[END EQUATION]**

 “Unknown days” refers to the difference between days in range and the maximum number of days that can be estimated from two measures. These are days that are neither in nor out of range. The percentage of days in range is then calculated using the approximation

**[INSERT EQUATION]**

**[END EQUATION]**

For example, in exhibit 15.7, we see six blood pressures measures, some in range and some out. In the first two measurements, the patient goes from a blood pressure of 125 to 150 (out of range). These two measures are 20 days apart; this patient is estimated to be in the range for 12 of these 20 days. Similar estimates are made for every two consecutive data. For thesecond and third measurement the estimate of days in the range is 20. If we assume that days more than two weeks away from the measurement are unknown days, then 6 out of these 20 days are unknown days. The last two measurements were both within range; there are 30 days between these measures, 16 of which are unknown days. The total number of days the patient is in the range is 77 (56 percent), and the total number of unknown days is 22.

**[INSERT EXHIBIT]**

**Exhibit 15.7** Calculation of Percentage of Days in Therapeutic Range

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Days Since Enrollment | Blood Pressure | Therapeutic Range | In Range | Days in Range | Unknown Days > Maximum of 14 Days |
|
| Lower | Upper  |
| 0 | 125 | 120 | 140 | Yes | 12 | 0 |
| 20 | 150 | 120 | 140 | No | 20 | 6 |
| 60 | 130 | 120 | 140 | Yes | 5 | 0 |
| 70 | 110 | 120 | 140 | No | 10 | 0 |
| 90 | 130 | 120 | 140 | Yes | 30 | 16 |
| 120 | 135 | 120 | 140 | Yes |  |  |
|  |  | Total Days in Range | 77 | 22 |
|  | Percentage of Days in Therapeutic Range | 56% |  |

**[END EXHIBIT]**

At least two observations over time are needed before the percentage of days in range can be calculated.

# [H1] Verification of Matching

Matching must be verified after patients are assigned to groups. If cases and controls are correctly matched, then all covariates (including combinations of covariates) must occur at the same rate in both groups—that is, little or no statistical difference appears on the covariates between cases and controls. In many studies, the verification of matching is made in error (Niven et al. 2012). A paired *t*-test can be done when cases have a 1:1 match to controls and have a symmetrical distribution. The Wilcoxon signed-rank test is used for measured nonparametric results with 1:1 matching. Linear or logistic regression is used to examine matched sets with matching that is not 1:1 (Breslow and Day 1980).

If the matching is not 1:1, the difference between each case and the mean of the three controls is calculated, then the average and the standard deviation of the differences are calculated. The *t*-statistic is used to test whether the mean of the calculated differences is significantly different from zero. If so, the null hypothesis is rejected, and the matching process has not led to equivalent groups. If equivalent groups are not available, the matching procedure is repeated until two statistically equivalent groups are identified.

# [H1] Analysis of Outcomes

Outcomes of case and control patients can be analyzed using the odds ratio of observed outcomes. First, the number of outcomes in cases and controls during the follow-up period are counted. Exhibit 15.8 shows the presence of these outcomes with positive symbols and absence with negative symbols. So and is the number of cases and controls that had positive outcomes. Likewise, and is the number of cases and controls that had negative outcomes.

**[INSERT EXHIBIT]**

**Exhibit 15.8** Contingency Table for Adverse Outcomes

|  |  |  |
| --- | --- | --- |
| Outcome = Fall | Cases | Controls |
| Yes | = 1 | = 1 |
| No | = 1 | = 3 |
| Total |  = 2 | = 4 |

**[END EXHIBIT]**

The probability of the outcomes among the cases is calculated as the ratio of the number of observed outcomes divided by the number of possible outcomes:

**[INSERT EQUATION]**

, and

.

**[END EQUATION]**

The odds ratio of positive outcomes is calculated as the ratio of these two probabilities and is written as

**[INSERT EQUATION]**

.

**[END EQUATION]**

An odds ratio greater than 1 suggests more positive outcomes among the cases than controls; an odds ratio less than 1 suggests the reverse. An odds ratio of 1 suggests that the probability of the positive outcomes in cases and controls is the same.

The odds ratio is a point estimate. It is useful to measure a confidence interval around this ratio. Confidence intervals are created so that the probability of the true odds ratio falling outside of the interval is small, say less than 5 percent. If there is a large number of cases in the study, the distribution of the natural log odds ratio, shown in the following formula as L, is approximately normal:

**[INSERT EQUATION]**

.

**[END EQUATION]**

In a normal distribution, 95 percent of the data would fall within 1.96 standard deviations of the mean. The standard deviation of the log of the odds ratio can be calculated as

**[INSERT EQUATION]**

.

**[END EQUATION]**

In a normal distribution, values that are more than 1.96 standard deviations away from the mean are considered relatively rare and occur less than 5 percent of the time. Therefore, the approximate 95 percent confidence interval for the population log odds ratio (Morris and Gardner 1988) can be estimated as

**[INSERT EQUATION]**

.

**[END EQUATION]**

These confidence limits are for the natural log of the odds ratio. The confidence limit for the odds ratio, itself, is calculated as

**[INSERT EQUATION]**

.

**[END EQUATION]**

If this confidence interval includes only numbers greater than 1.0, the hypothesis that cases and controls have the same outcome has less than a 5 percent chance of occurrence. Then, one could reject the hypothesis of no difference between the groups with relative confidence.

The procedure we have outlined shows how the statistical significance of the difference between cases and controls is examined. The opposite can also be true. A confidence limit that includes only numbers less than 1.0 will also indicate a statistically significance difference between the groups. The direction and interpretation of the odds ratio must be done with care relative to the desired and anticipated treatment effect.

 Exhibit 15.9 applies these concepts to our data. Clearly, we have very few cases and controls and one would not expect the findings to be either significant or appropriate for test of confidence interval. We apply the proposed method to these data only to explain the use of the formulas. We can examine the outcomes during the follow-up period among cases (i.e., 1 and 3) and controls (i.e., 2, 4, 8, and 9). From data in exhibit 15.9, the test statistic *l* is calculated as

**[INSERT EQUATION]**

 = (−2.5, 4.7).

**[END EQUATION]**

This confidence interval must now be translated back into the original study units, so

**[INSERT EQUATION]**

Confidence interface = (, = (0.1, 107.4).

**[END EQUATION]**

The confidence interval for the ratio includes 1. Therefore, the hypothesis of significant difference between cases and controls cannot be rejected.

**[INSERT EXHIBIT]**

**Exhibit 15.9** Calculation of Odds Ratio for Example Cases and Controls

|  |  |  |
| --- | --- | --- |
| Outcome | Cases | Controls |
| Yes | 1 | 1 |
| No | 1 | 3 |
| Total | 2 | 4 |
|  |  |  |
|  |  |  |
| L  | 1.1 |  |
| Variance  | 2.08 |  |
| Standard deviation  | 1.44 |  |
| 1.96 Standard deviation P | 3.58 |  |
| Upper limit | 107.45 |  |
| Lower limit | 0.08 |  |

**[END EXHIBIT]**

Many policymakers prefer visual displays. Typically one plots the data using the probability of the outcome before and after enrollment. Before enrollment in the program, the rate is 50 percent positive for cases and 50 percent positive for controls. This is the overlapping point in exhibit 15.10, and it shows that before enrollment in the program, cases and controls had the same rate of falls. In the follow-up period, the percentage of patients experiencing a fall changes. Both groups have a decline in the rate of falls, but the decline is more in the cases than controls.

**[INSERT EXHIBIT]**

**Exhibit 15.10** Impact of Enrollment in Program on Patient Falls

**[END EXHIBIT]**

The problem with exhibit 15.10 is that it does not show the period that elapses before a fall occurs. Because adverse outcomes (death) often happen over lengthy periods, it can be important to report time until the event.

# [H1] Analysis of Time to Event

Sometimes the outcome of interest is not a count of events (e.g., falls), but days, or in our case, months to the event (person-time). The analysis of outcomes over time can be done using a Kaplan-Meier estimator (Kaplan and Meier 1958). The estimator can be used to examine statistical significance and to report time until outcome. An advantage of using this estimator is that it can accommodate changes in the experience of patients in the study. For example, if patients die before the outcome of interest is measured, they can be left out of the calculation for periods after their death. In addition, if patients change their places of care, they can be excluded from the study from the time that they changed providers and location of treatment.

For example, during each period, the number of patients at risk of falling (the number of patients in the study minus the patients who are removed) and the number of patients that do not fall (number at risk minus number that have fallen) are calculated. This is the conditional probability of falling given that the patient has not fallen in prior periods. The probability of falling in the period is calculated as the probability of falling in a past period multiplied by the conditional probability of not falling. Exhibit 15.11 shows the calculation of these probabilities for our data. Among the two cases, there was one fall in the third month. Among the four controls, there was one fall in the second month. There was one patient in the control group that died in the first month and therefore was not available to the study in subsequent months.

**[INSERT EXHIBIT]**

**Exhibit 15.11** Probability of Falling at Different Periods

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Period** | **Number at Risk** | **Number Removed** | **Number Fell** | **Number No Fall** | **No Fall Probability** |
| Cases | 1 | 2 | 0 | 0 | 2 | 1 |
| 2 | 2 | 0 | 0 | 2 | 1 |
| 3 | 2 | 0 | 1 | 1 | 0.5 |
| Controls | 1 | 4 | 1 | 0 | 4 | 1 |
| 2 | 3 | 0 | 1 | 2 | 0.67 |
| 3 | 2 | 0 | 0 | 2 | 0.67 |

 **[END EXHIBIT]**

 Exhibit 15.12 shows the resulting percentage of patients having no falls at different time intervals. Cases had a fall sooner than the controls. The statistical significance of differences in rates of falls over time can be established with the variance for the Kaplan-Meier statistic.

**[INSERT EXHIBIT]**

**Exhibit 15.12** Impact of Enrollment on Months to Falls

**[END EXHIBIT]**

#  [H1] Overlap

Case control methods can lead to erroneous conclusions in a number of ways. If the matching is not focused on the correct control variables, findings may be distorted. Even if matching is focused on the right variables but too few cases or controls are matched, the process has potential for error. Sometimes, a large portion of cases occurs only once or is never matched with any controls. In these situations, the findings from the cases that are matched may not generalize to the type of cases that are not matched. The percentage of cases that are matched to at least one control is referred to as overlap between cases and control. When the overlap is less than 80 percent, there is concern with generalizability of the findings.

# [H1] Summary

This chapter has described how matched case controls can be organized and applied to data in EHRs. These types of studies control for a number of possible ways in which observational studies may lead to erroneous conclusions. As a quasi-experimental design should, the matched case control protects against extraneous variables that affect both cases and controls. The effect of time and enrollment periods also can be appropriately handled.

Unfortunately, a matched case control design is not necessarily superior to a study design that uses unmatched controls. Indiscriminate matching on complications of treatment can eliminate the true treatment effect. Selection of study design should be done after careful consideration and discussion of the possible effects of the selection of study variables on measurement of clinicaloutcomes. As in most good epidemiological studies, statistical analyses must be informed by clinical insights. Careful steps should be taken not to match on variables on the causal path from treatment to outcome (e.g., complication of treatment).

# [H1] Supplemental Resources

A problem set, solutions to problems, multimedia presentations, SQL code, and other related material are on the course website.

**[H1] References**

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1. Patient falls were classified using the following E codes in the International Classification of Disease: E8800 E8801 E8809 E8810 E8811 E882 E8830 E8831 E8832 E8839 E8840 E8841 E8842 E8843 E8844 E8845 E8846 E8849 E885 E8850 E8851 E8852 E8853 E8854 E8859 E8860 E8869 E888 E8880 E8881 E8888 E8889 E9681 E9870 E9871 E9872 E9879. [↑](#endnote-ref-1)
2. Patient injuries were measured using the following codes: 7960 7990 79901 79902 9071 9073 9074 9075 9079 9085 9086 9089 9092 9094 9099 9300 9301 9302 9308 9309 931 932 9330 9331 9340 9341 9348 9349 9350 9351 9352 936 937 938 9390 9391 9392 9393 9399 9500 9501 9502 9503 9509 9510 9511 9512 9513 9514 9515 9516 9517 9518 9519 9530 9531 9532 9533 9534 9535 9538 9539 9540 9541 9548 9549 9550 9551 9552 9553 9554 9555 9556 9557 9558 9559 9560 9561 9562 9563 9564 9565 9568 9569 9570 9571 9578 9579 9580 9581 9582 9583 9584 9585 9586 9587 9588 95890 95891 95892 95893 95899 9590 95901 95909 9591 95911 95912 95913 95914 95919 9592 9593 9594 9595 9596 9597 9598 9599 990 9910 9911 9912 9913 9914 9915 9916 9918 9919 9920 9921 9922 9923 9924 9925 9926 9927 9928 9929 9930 9931 9932 9933 9934 9938 9939 9940 9941 9942 9943 9944 9945 9946 9947 9948 9949 9951 9955 99550 99551 99552 99553 99554 99555 99559 99580 99581 99582 99583 99584 99585 99589 99590 99591 99592 99593 99594 V155 V1551 V1559 V156 V1588 V713 V714 V715 V716 V9010 V9011 V9012 V902 V9031 V9032 V9033 V9039 V9081 V9083 V9089 V909. [↑](#endnote-ref-2)
3. The following codes were used to determine whether the patient has had an adverse medication effect: E9300 E9301 E9302 E9303 E9304 E9305 E9306 E9307 E9308 E9309 E9310 E9311 E9312 E9313 E9314 E9315 E9316 E9317 E9318 E9319 E9320 E9321 E9322 E9323 E9324 E9325 E9326 E9327 E9328 E9329 E9330 E9331 E9332 E9333 E9334 E9335 E9336 E9337 E9338 E9339 E9340 E9341 E9342 E9343 E9344 E9345 E9346 E9347 E9348 E9349 E9350 E9351 E9352 E9353 E9354 E9355 E9356 E9357 E9358 E9359 E9360 E9361 E9362 E9363 E9364 E9370 E9371 E9372 E9373 E9374 E9375 E9376 E9378 E9379 E9380 E9381 E9382 E9383 E9384 E9385 E9386 E9387 E9389 E9390 E9391 E9392 E9393 E9394 E9395 E9396 E9397 E9398 E9399 E9400 E9401 E9408 E9409 E9410 E9411 E9412 E9413 E9419 E9420 E9421 E9422 E9423 E9424 E9425 E9426 E9427 E9428 E9429 E9430 E9431 E9432 E9433 E9434 E9435 E9436 E9438 E9439 E9440 E9441 E9442 E9443 E9444 E9445 E9446 E9447 E9450 E9451 E9452 E9453 E9454 E9455 E9456 E9457 E9458 E9460 E9461 E9462 E9463 E9464 E9465 E9466 E9467 E9468 E9469 E9470 E9471 E9472 E9473 E9474 E9478 E9479 E9480 E9481 E9482 E9483 E9484 E9485 E9486 E9488 E9489 E9490 E9491 E9492 E9493 E9494 E9495 E9496 E9497 E9499. [↑](#endnote-ref-3)
4. The following codes were used to determine mood disorders: 29383 29600 29601 29602 29603 29604 29605 29606 29610 29611 29612 29613 29614 29615 29616 29620 29621 29622 29623 29624 29625 29626 29630 29631 29632 29633 29634 29635 29636 29640 29641 29642 29643 29644 29645 29646 29650 29651 29652 29653 29654 29655 29656 29660 29661 29662 29663 29664 29665 29666 2967 29680 29681 29682 29689 29690 29699 3004 311. The following codes were used to identify anxiety disorders: 29384 30000 30001 30002 30009 30010 30020 30021 30022 30023 30029 3003 3005 30089 3009 3080 3081 3082 3083 3084 3089 30981 3130 3131 31321 31322 3133 31382 31383. [↑](#endnote-ref-4)