Chapter 10

Methods for Comparative Studies

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10.1 Introduction
In eHealth evaluation, comparative studies aim to find out whether group differences in eHealth system adoption make a difference in important outcomes. These groups may differ in their composition, the type of system in use, and the setting where they work over a given time duration. The comparisons are to determine whether significant differences exist for some predefined measures between these groups, while controlling for as many of the conditions as possible such as the composition, system, setting and duration.

According to the typology by Friedman and Wyatt (2006), comparative studies take on an objective view where events such as the use and effect of an eHealth system can be defined, measured and compared through a set of variables to prove or disprove a hypothesis. For comparative studies, the design options are experimental versus observational and prospective versus retrospective. The quality of eHealth comparative studies depends on such aspects of methodological design as the choice of variables, sample size, sources of bias, confounders, and adherence to quality and reporting guidelines.

In this chapter we focus on experimental studies as one type of comparative study and their methodological considerations that have been reported in the eHealth literature. Also included are three case examples to show how these studies are done.

10.2 Types of Comparative Studies
Experimental studies are one type of comparative study where a sample of participants is identified and assigned to different conditions for a given time duration, then compared for differences. An example is a hospital with two care
units where one is assigned a CPOE system to process medication orders electronically while the other continues its usual practice without a CPOE. The participants in the unit assigned to the CPOE are called the intervention group and those assigned to usual practice are the control group. The comparison can be performance or outcome focused, such as the ratio of correct orders processed or the occurrence of adverse drug events in the two groups during the given time period. Experimental studies can take on a randomized or non-randomized design. These are described below.

### 10.2.1 Randomized Experiments

In a randomized design, the participants are randomly assigned to two or more groups using a known randomization technique such as a random number table. The design is prospective in nature since the groups are assigned concurrently, after which the intervention is applied then measured and compared. Three types of experimental designs seen in eHealth evaluation are described below (Friedman & Wyatt, 2006; Zwarenstein & Treweek, 2009).

*Randomized controlled trials (RCTs)* – In RCTs participants are randomly assigned to an intervention or a control group. The randomization can occur at the patient, provider or organization level, which is known as the unit of allocation. For instance, at the patient level one can randomly assign half of the patients to receive EMR reminders while the other half do not. At the provider level, one can assign half of the providers to receive the reminders while the other half continues with their usual practice. At the organization level, such as a multisite hospital, one can randomly assign EMR reminders to some of the sites but not others.

*Cluster randomized controlled trials (CRCTs)* – In CRCTs, clusters of participants are randomized rather than by individual participants since they are found in naturally occurring groups such as living in the same communities. For instance, clinics in one city may be randomized as a cluster to receive EMR reminders while clinics in another city continue their usual practice.

*Pragmatic trials* – Unlike RCTs that seek to find out if an intervention such as a CPOE system works under ideal conditions, pragmatic trials are designed to find out if the intervention works under usual conditions. The goal is to make the design and findings relevant to and practical for decision-makers to apply in usual settings. As such, pragmatic trials have few criteria for selecting study participants, flexibility in implementing the intervention, usual practice as the comparator, the same compliance and follow-up
intensity as usual practice, and outcomes that are relevant to decision-makers.

10.2.2 Non-randomized Experiments

Non-randomized design is used when it is neither feasible nor ethical to randomize participants into groups for comparison. It is sometimes referred to as a quasi-experimental design. The design can involve the use of prospective or retrospective data from the same or different participants as the control group. Three types of non-randomized designs are described below (Harris et al., 2006).

*Intervention group only with pretest and post-test design* – This design involves only one group where a pretest or baseline measure is taken as the control period, the intervention is implemented, and a post-test measure is taken as the intervention period for comparison. For example, one can compare the rates of medication errors before and after the implementation of a CPOE system in a hospital. To increase study quality, one can add a second pretest period to decrease the probability that the pretest and posttest difference is due to chance, such as an unusually low medication error rate in the first pretest period. Other ways to increase study quality include adding an unrelated outcome such as patient case-mix that should not be affected, removing the intervention to see if the difference remains, and removing then re-implementing the intervention to see if the differences vary accordingly.

*Intervention and control groups with post-test design* – This design involves two groups where the intervention is implemented in one group and compared with a second group without the intervention, based on a post-test measure from both groups. For example, one can implement a CPOE system in one care unit as the intervention group with a second unit as the control group and compare the post-test medication error rates in both units over six months. To increase study quality, one can add one or more pretest periods to both groups, or implement the intervention to the control group at a later time to measure for similar but delayed effects.

*Interrupted time series (ITS) design* – In ITS design, multiple measures are taken from one group in equal time intervals, interrupted by the implementation of the intervention. The multiple pretest and post-test measures decrease the probability that the differences detected are due to chance or unrelated effects. An example is to take six consecutive monthly medication error rates as the pretest measures, implement the CPOE system, then take another
six consecutive monthly medication error rates as the post-test measures for comparison in error rate differences over 12 months. To increase study quality, one may add a concurrent control group for comparison to be more convinced that the intervention produced the change.

10.3 Methodological Considerations
The quality of comparative studies is dependent on their internal and external validity. Internal validity refers to the extent to which conclusions can be drawn correctly from the study setting, participants, intervention, measures, analysis and interpretations. External validity refers to the extent to which the conclusions can be generalized to other settings. The major factors that influence validity are described below.

10.3.1 Choice of Variables
Variables are specific measurable features that can influence validity. In comparative studies, the choice of dependent and independent variables and whether they are categorical and/or continuous in values can affect the type of questions, study design and analysis to be considered. These are described below (Friedman & Wyatt, 2006).

*Dependent variables* – This refers to outcomes of interest; they are also known as outcome variables. An example is the rate of medication errors as an outcome in determining whether CPOE can improve patient safety.

*Independent variables* – This refers to variables that can explain the measured values of the dependent variables. For instance, the characteristics of the setting, participants and intervention can influence the effects of CPOE.

*Categorical variables* – This refers to variables with measured values in discrete categories or levels. Examples are the type of providers (e.g., nurses, physicians and pharmacists), the presence or absence of a disease, and pain scale (e.g., 0 to 10 in increments of 1). Categorical variables are analyzed using non-parametric methods such as chi-square and odds ratio.

*Continuous variables* – This refers to variables that can take on infinite values within an interval limited only by the desired precision. Examples are blood pressure, heart rate and body temperature. Continuous variables are analyzed using parametric methods such as t-test, analysis of variance or multiple regression.
10.3.2 Sample Size

Sample size is the number of participants to include in a study. It can refer to patients, providers or organizations depending on how the unit of allocation is defined. There are four parts to calculating sample size. They are described below (Noordzij et al., 2010).

**Significance level** – This refers to the probability that a positive finding is due to chance alone. It is usually set at 0.05, which means having a less than 5% chance of drawing a false positive conclusion.

**Power** – This refers to the ability to detect the true effect based on a sample from the population. It is usually set at 0.8, which means having at least an 80% chance of drawing a correct conclusion.

**Effect size** – This refers to the minimal clinically relevant difference that can be detected between comparison groups. For continuous variables, the effect is a numerical value such as a 10-kilogram weight difference between two groups. For categorical variables, it is a percentage such as a 10% difference in medication error rates.

**Variability** – This refers to the population variance of the outcome of interest, which is often unknown and is estimated by way of standard deviation (SD) from pilot or previous studies for continuous outcome.

<table>
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<tr>
<th>Continuous variable</th>
<th>Categorical variable</th>
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<td>( n = \frac{2[(a+b)\sigma^2]}{(\mu_1-\mu_2)^2} ) where</td>
<td>( n = \frac{[(a+b)(p_1q_1+p_2q_2)]}{\chi^2} )</td>
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<td>( n = \text{sample size for each group} )</td>
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<td>( \mu_1-\mu_2 = \text{desired difference between groups} )</td>
<td>( p_2 = \text{proportion of participants with condition in group 2} )</td>
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<td>( \sigma = \text{population variance} )</td>
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An example of sample size calculation for an RCT to examine the effect of CDS on improving systolic blood pressure of hypertensive patients is provided
in the Appendix. Refer to the Biomath website from Columbia University (n.d.) for a simple Web-based sample size / power calculator.

10.3.3 Sources of Bias
There are five common sources of biases in comparative studies. They are selection, performance, detection, attrition and reporting biases (Higgins & Green, 2011). These biases, and the ways to minimize them, are described below (Vervloet et al., 2012).

Selection or allocation bias – This refers to differences between the composition of comparison groups in terms of the response to the intervention. An example is having sicker or older patients in the control group than those in the intervention group when evaluating the effect of EMR reminders. To reduce selection bias, one can apply randomization and concealment when assigning participants to groups and ensure their compositions are comparable at baseline.

Performance bias – This refers to differences between groups in the care they received, aside from the intervention being evaluated. An example is the different ways by which reminders are triggered and used within and across groups such as electronic, paper and phone reminders for patients and providers. To reduce performance bias, one may standardize the intervention and blind participants from knowing whether an intervention was received and which intervention was received.

Detection or measurement bias – This refers to differences between groups in how outcomes are determined. An example is where outcome assessors pay more attention to outcomes of patients known to be in the intervention group. To reduce detection bias, one may blind assessors from participants when measuring outcomes and ensure the same timing for assessment across groups.

Attrition bias – This refers to differences between groups in ways that participants are withdrawn from the study. An example is the low rate of participant response in the intervention group despite having received reminders for follow-up care. To reduce attrition bias, one needs to acknowledge the dropout rate and analyze data according to an intent-to-treat principle (i.e., include data from those who dropped out in the analysis).
Reporting bias – This refers to differences between reported and unreported findings. Examples include biases in publication, time lag, citation, language and outcome reporting depending on the nature and direction of the results. To reduce reporting bias, one may make the study protocol available with all pre-specified outcomes and report all expected outcomes in published results.

10.3.4 Confounders
Confounders are factors other than the intervention of interest that can distort the effect because they are associated with both the intervention and the outcome. For instance, in a study to demonstrate whether the adoption of a medication order entry system led to lower medication costs, there can be a number of potential confounders that can affect the outcome. These may include severity of illness of the patients, provider knowledge and experience with the system, and hospital policy on prescribing medications (Harris et al., 2006). Another example is the evaluation of the effect of an antibiotic reminder system on the rate of post-operative deep venous thromboses (DVTs). The confounders can be general improvements in clinical practice during the study such as prescribing patterns and post-operative care that are not related to the reminders (Friedman & Wyatt, 2006).

To control for confounding effects, one may consider the use of matching, stratification and modelling. Matching involves the selection of similar groups with respect to their composition and behaviours. Stratification involves the division of participants into subgroups by selected variables, such as comorbidity index to control for severity of illness. Modelling involves the use of statistical techniques such as multiple regression to adjust for the effects of specific variables such as age, sex and/or severity of illness (Higgins & Green, 2011).

10.3.5 Guidelines on Quality and Reporting
There are guidelines on the quality and reporting of comparative studies. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) guidelines provide explicit criteria for rating the quality of studies in randomized trials and observational studies (Guyatt et al., 2011). The extended CONSORT (Consolidated Standards of Reporting Trials) Statements for non-pharmacologic trials (Boutron, Moher, Altman, Schulz, & Ravaud, 2008), pragmatic trials (Zwarestein et al., 2008), and eHealth interventions (Baker et al., 2010) provide reporting guidelines for randomized trials.

The GRADE guidelines offer a system of rating quality of evidence in systematic reviews and guidelines. In this approach, to support estimates of intervention effects RCTs start as high-quality evidence and observational studies as low-quality evidence. For each outcome in a study, five factors may rate down the quality of evidence. The final quality of evidence for each outcome would fall into one of high, moderate, low, and very low quality. These factors are listed below (for more details on the rating system, refer to Guyatt et al., 2011).
Design limitations – For RCTs they cover the lack of allocation concealment, lack of blinding, large loss to follow-up, trial stopped early or selective outcome reporting.

Inconsistency of results – Variations in outcomes due to unexplained heterogeneity. An example is the unexpected variation of effects across subgroups of patients by severity of illness in the use of preventive care reminders.

Indirectness of evidence – Reliance on indirect comparisons due to restrictions in study populations, intervention, comparator or outcomes. An example is the 30-day readmission rate as a surrogate outcome for quality of computer-supported emergency care in hospitals.

Imprecision of results – Studies with small sample size and few events typically would have wide confidence intervals and are considered of low quality.

Publication bias – The selective reporting of results at the individual study level is already covered under design limitations, but is included here for completeness as it is relevant when rating quality of evidence across studies in systematic reviews.

The original CONSORT Statement has 22 checklist items for reporting RCTs. For non-pharmacologic trials extensions have been made to 11 items. For pragmatic trials extensions have been made to eight items. These items are listed below. For further details, readers can refer to Boutron and colleagues (2008) and the CONSORT website (CONSORT, n.d.).

Title and abstract – one item on the means of randomization used.

Introduction – one item on background, rationale, and problem addressed by the intervention.

Methods – 10 items on participants, interventions, objectives, outcomes, sample size, randomization (sequence generation, allocation concealment, implementation), blinding (masking), and statistical methods.

Results – seven items on participant flow, recruitment, baseline data, numbers analyzed, outcomes and estimation, ancillary analyses, adverse events.
Discussion – three items on interpretation, generalizability, overall evidence.

The CONSORT Statement for eHealth interventions describes the relevance of the CONSORT recommendations to the design and reporting of eHealth studies with an emphasis on Internet-based interventions for direct use by patients, such as online health information resources, decision aids and PHRs. Of particular importance is the need to clearly define the intervention components, their role in the overall care process, target population, implementation process, primary and secondary outcomes, denominators for outcome analyses, and real world potential (for details refer to Baker et al., 2010).

10.4 Case Examples

10.4.1 Pragmatic RCT in Vascular Risk Decision Support
Holbrook and colleagues (2011) conducted a pragmatic RCT to examine the effects of a CDS intervention on vascular care and outcomes for older adults. The study is summarized below.

Setting – Community-based primary care practices with EMRs in one Canadian province.

Participants – English-speaking patients 55 years of age or older with diagnosed vascular disease, no cognitive impairment and not living in a nursing home, who had a provider visit in the past 12 months.

Intervention – A Web-based individualized vascular tracking and advice CDS system for eight top vascular risk factors and two diabetic risk factors, for use by both providers and patients and their families. Providers and staff could update the patient’s profile at any time and the CDS algorithm ran nightly to update recommendations and colour highlighting used in the tracker interface. Intervention patients had Web access to the tracker, a print version mailed to them prior to the visit, and telephone support on advice.

Design – Pragmatic, one-year, two-arm, multicentre RCT, with randomization upon patient consent by phone, using an allocation-concealed online program. Randomization was by patient with stratification by provider using a block size of six. Trained reviewers examined EMR data and conducted patient telephone interviews to collect risk factors, vascular history, and vascular events. Providers completed questionnaires on the intervention at study
end. Patients had final 12-month lab checks on urine albumin, low-density lipoprotein cholesterol, and A1c levels.

Outcomes – Primary outcome was based on change in process composite score (PCS) computed as the sum of frequency-weighted process score for each of the eight main risk factors with a maximum score of 27. The process was considered met if a risk factor had been checked. PCS was measured at baseline and study end with the difference as the individual primary outcome scores. The main secondary outcome was a clinical composite score (CCS) based on the same eight risk factors compared in two ways: a comparison of the mean number of clinical variables on target and the percentage of patients with improvement between the two groups. Other secondary outcomes were actual vascular event rates, individual PCS and CCS components, ratings of usability, continuity of care, patient ability to manage vascular risk, and quality of life using the EuroQol five dimensions questionnaire (EQ-5D).

Analysis – 1,100 patients were needed to achieve 90% power in detecting a one-point PCS difference between groups with a standard deviation of five points, two-tailed t-test for mean difference at 5% significance level, and a withdrawal rate of 10%. The PCS, CCS and EQ-5D scores were analyzed using a generalized estimating equation accounting for clustering within providers. Descriptive statistics and χ2 tests or exact tests were done with other outcomes.

Findings – 1,102 patients and 49 providers enrolled in the study. The intervention group with 545 patients had significant PCS improvement with a difference of 4.70 ($p < .001$) on a 27-point scale. The intervention group also had significantly higher odds of rating improvements in their continuity of care (4.178, $p < .001$) and ability to improve their vascular health (3.07, $p < .001$). There was no significant change in vascular events, clinical variables and quality of life. Overall the CDS intervention led to reduced vascular risks but not to improved clinical outcomes in a one-year follow-up.

10.4.2 Non-randomized Experiment in Antibiotic Prescribing in Primary Care
Mainous, Lambourne, and Nietert (2013) conducted a prospective non-randomized trial to examine the impact of a CDS system on antibiotic prescribing for acute respiratory infections (ARIs) in primary care. The study is summarized below.
Setting – A primary care research network in the United States whose members use a common EMR and pool data quarterly for quality improvement and research studies.

Participants – An intervention group with nine practices across nine states, and a control group with 61 practices.

Intervention – Point-of-care CDS tool as customizable progress note templates based on existing EMR features. CDS recommendations reflect Centre for Disease Control and Prevention (CDC) guidelines based on a patient’s predominant presenting symptoms and age. CDS was used to assist in ARI diagnosis, prompt antibiotic use, record diagnosis and treatment decisions, and access printable patient and provider education resources from the CDC.

Design – The intervention group received a multi-method intervention to facilitate provider CDS adoption that included quarterly audit and feedback, best practice dissemination meetings, academic detailing site visits, performance review and CDS training. The control group did not receive information on the intervention, the CDS or education. Baseline data collection was for three months with follow-up of 15 months after CDS implementation.

Outcomes – The outcomes were frequency of inappropriate prescribing during an ARI episode, broad-spectrum antibiotic use and diagnostic shift. Inappropriate prescribing was computed by dividing the number of ARI episodes with diagnoses in the inappropriate category that had an antibiotic prescription by the total number of ARI episodes with diagnosis for which antibiotics are inappropriate. Broad-spectrum antibiotic use was computed by all ARI episodes with a broad-spectrum antibiotic prescription by the total number of ARI episodes with an antibiotic prescription. Antibiotic drift was computed in two ways: dividing the number of ARI episodes with diagnoses where antibiotics are appropriate by the total number of ARI episodes with an antibiotic prescription; and dividing the number of ARI episodes where antibiotics were inappropriate by the total number of ARI episodes. Process measure included frequency of CDS template use and whether the outcome measures differed by CDS usage.

Analysis – Outcomes were measured quarterly for each practice, weighted by the number of ARI episodes during the quarter to assign greater weight to practices with greater numbers of relevant episodes and to periods with greater numbers of relevant episodes.
Weighted means and 95% CIs were computed separately for adult and pediatric (less than 18 years of age) patients for each time period for both groups. Baseline means in outcome measures were compared between the two groups using weighted independent-sample *t*-tests. Linear mixed models were used to compare changes over the 18-month period. The models included time, intervention status, and were adjusted for practice characteristics such as specialty, size, region and baseline ARIs. Random practice effects were included to account for clustering of repeated measures on practices over time. *P*-values of less than 0.05 were considered significant.

**Findings** – For adult patients, inappropriate prescribing in ARI episodes declined more among the intervention group (-0.6%) than the control group (4.2%)(*p = 0.03*), and prescribing of broad-spectrum antibiotics declined by 16.6% in the intervention group versus an increase of 1.1% in the control group (*p < 0.0001*). For pediatric patients, there was a similar decline of 19.7% in the intervention group versus an increase of 0.9% in the control group (*p < 0.0001*). In summary, the CDS had a modest effect in reducing inappropriate prescribing for adults, but had a substantial effect in reducing the prescribing of broad-spectrum antibiotics in adult and pediatric patients.

### 10.4.3 Interrupted Time Series on EHR Impact in Nursing Care

Dowding, Turley, and Garrido (2012) conducted a prospective ITS study to examine the impact of EHR implementation on nursing care processes and outcomes. The study is summarized below.

**Setting** – Kaiser Permanente (KP) as a large not-for-profit integrated healthcare organization in the United States.

**Participants** – 29 KP hospitals in the northern and southern regions of California.

**Intervention** – An integrated EHR system implemented at all hospitals with CPOE, nursing documentation and risk assessment tools. The nursing component for risk assessment documentation of pressure ulcers and falls was consistent across hospitals and developed by clinical nurses and informaticists by consensus.

**Design** – ITS design with monthly data on pressure ulcers and quarterly data on fall rates and risk collected over seven years be-
between 2003 and 2009. All data were collected at the unit level for each hospital.

**Outcomes** – Process measures were the proportion of patients with a fall risk assessment done and the proportion with a hospital-acquired pressure ulcer (HAPU) risk assessment done within 24 hours of admission. Outcome measures were fall and HAPU rates as part of the unit-level nursing care process and nursing sensitive outcome data collected routinely for all California hospitals. Fall rate was defined as the number of unplanned descents to the floor per 1,000 patient days, and HAPU rate was the percentage of patients with stages I-IV or unstageable ulcer on the day of data collection.

**Analysis** – Fall and HAPU risk data were synchronized using the month in which the EHR was implemented at each hospital as time zero and aggregated across hospitals for each time period. Multivariate regression analysis was used to examine the effect of time, region and EHR.

**Findings** – The EHR was associated with significant increase in document rates for HAPU risk (2.21; 95% CI 0.67 to 3.75) and non-significant increase for fall risk (0.36; -3.58 to 4.30). The EHR was associated with 13% decrease in HAPU rates (-0.76; -1.37 to -0.16) but no change in fall rates (-0.091; -0.29 to 0.11). Hospital region was a significant predictor of variation for HAPU (0.72; 0.30 to 1.14) and fall rates (0.57; 0.41 to 0.72). During the study period, HAPU rates decreased significantly (-0.16; -0.20 to -0.13) but not fall rates (0.0052; -0.01 to 0.02). In summary, EHR implementation was associated with a reduction in the number of HAPUs but not patient falls, and changes over time and hospital region also affected outcomes.

**10.5 Summary**
In this chapter we introduced randomized and non-randomized experimental designs as two types of comparative studies used in eHealth evaluation. Randomization is the highest quality design as it reduces bias, but it is not always feasible. The methodological issues addressed include choice of variables, sample size, sources of biases, confounders, and adherence to reporting guidelines. Three case examples were included to show how eHealth comparative studies are done.
References


Example of Sample Size Calculation

This is an example of sample size calculation for an RCT that examines the effect of a CDS system on reducing systolic blood pressure in hypertensive patients. The case is adapted from the example described in the publication by Noordzij et al. (2010).

(a) Systolic blood pressure as a continuous outcome measured in mmHg

Based on similar studies in the literature with similar patients, the systolic blood pressure values from the comparison groups are expected to be normally distributed with a standard deviation of 20 mmHg. The evaluator wishes to detect a clinically relevant difference of 15 mmHg in systolic blood pressure as an outcome between the intervention group with CDS and the control group without CDS. Assuming a significance level or alpha of 0.05 for 2-tailed t-test and power of 0.80, the corresponding multipliers are 1.96 and 0.842, respectively. Using the sample size equation for continuous outcome below we can calculate the sample size needed for the above study.

\[ n = \frac{2(1.96 + 0.842)^2(20^2)}{15^2} \]

Providing the values in the equation would give the sample size (n) of 28 samples per group as the result

(b) Systolic blood pressure as a categorical outcome measured as below or above 140 mmHg (i.e., hypertension yes/no)

In this example a systolic blood pressure from a sample that is above 140 mmHg is considered an event of the patient with hypertension. Based on published literature the proportion of patients in the general population with hypertension is 30%. The evaluator wishes to detect a clinically relevant difference

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1 From Table 3 on p. 1392 of Noordzij et al. (2010).
of 10% in systolic blood pressure as an outcome between the intervention group with CDS and the control group without CDS. This means the expected proportion of patients with hypertension is 20% ($p_1 = 0.2$) in the intervention group and 30% ($p_2 = 0.3$) in the control group. Assuming a significance level or alpha of 0.05 for 2-tailed $t$-test and power of 0.80 the corresponding multipliers are 1.96 and 0.842, respectively. Using the sample size equation for categorical outcome below, we can calculate the sample size needed for the above study.

$$n = \frac{[(a+b)^2(p_1q_1+p_2q_2)]}{\chi^2}$$

$n =$ sample size for each group

$p_1 =$ proportion of patients with hypertension in intervention group

$q_1 =$ proportion of patients without hypertension in intervention group (or $1-p_1$)

$p_2 =$ proportion of patients with hypertension in control group

$q_2 =$ proportion of patients without hypertension in control group (or $1-p_2$)

$\chi =$ desired difference in proportion of hypertensive patients between two groups

$a =$ multiplier for significance level (or alpha)

$b =$ multiplier for power (or $1$-beta)

Providing the values in the equation would give the sample size ($n$) of 291 samples per group as the result

$$n = \frac{[(1.96+0.842)^2((0.2)(0.8)+(0.3)(0.7))]}/(0.1)^2$$

or 291 samples per group.