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FACTORS ASSOCIATED WITH PATIENT ATTRITION: FINDINGS FROM TWO CLINICAL TRIALS OF COGNITIVE BEHAVIORAL INTERVENTIONS

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FACTORS ASSOCIATED WITH PATIENT ATTRITION: FINDINGS FROM TWO CLINICAL TRIALS OF COGNITIVE BEHAVIORAL INTERVENTIONS

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ABSTRACT

FACTORS ASSOCIATED WITH PATIENT ATTRITION: FINDINGS FROM TWO CLINICAL TRIALS OF COGNITIVE BEHAVIORAL INTERVENTIONS

By

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Randomized clinical trials and prospective observational studies are quality epidemiological study designs for evaluating treatments and for studying the outcomes of an exposure. Patent attrition from these studies is a potential threat to their validity. If potential drop-outs can be identified early in a study, then researchers can design strategies specifically targeting such patients to at least minimize their attrition. This research was carried out on data from two clinical trials of cognitive behavioral interventions to identify factors associated with patient who dropped out prematurely.

In the first study 719 patients, of acute coronary syndrome (ACS), admitted to one of the five participating mid-Michigan hospitals were recruited. Following discharge, patients were approached by telephone at one-month baseline (n=525), 3 months (n=440), and 8 months (n=388). Following baseline interview patients were randomized to either a standard treatment arm or to standard treatment plus a cognitive intervention arm. Attrition of patients, following baseline interview (failure to complete the next scheduled interview) was modeled using a Generalized Estimating Equation (GEE) model, on a data set with multiple records per patient.

The second data set is a group of cancer patients undergoing chemotherapy, at one of the six different hospitals in Michigan, Indiana and Ohio. Two hundred and sixty three patients consented to participate. Data collection was done at baseline (n=235), 10 weeks (n=178), 20 weeks (n=139), and 32 weeks (n= 125). Attrition following baseline was modeled in the same manner as for the cardiac patients.

Age of the patient, smoking habits, depression and abstinence from alcohol were found to have an association with attrition in cardiac patients. Whereas among cancer patients, cancer of lung, time spent in trial, depression and education were found to significantly influence attrition.

Patient attrition from longitudinal studies is mostly a function of their mental heath, social activity and support. Non-conformation with the expected role of the patient given the intervention under study in the trial also influences patients' chances of dropping out prematurely.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS USED

ACS	Acute Coronary Syndrome
AOR	Adjusted Odds ratio
ASI	Activity Status Index
CCI	Charlson Comorbidity Index
CES-D	Centers for Epidemiologic Studies Depression scale
CI	Confidence Interval
EF	Left Ventricular Ejection Fraction (Left Ventricle)
FHCC	Family Home Care for Cancer
GEE	Generalized Estimating Equation
HARP	Heart After-Hospital Recovery Planner
IPPSR	Institute for Public Policy and Social Research
IRB	Institutional Review Board
MRC CFAS	Medical Research Council Cognitive Function and Aging Study
MSU	Michigan State University
QLMI	Quality of Life after Myocardial infarction
SD	Standard Deviation
SES	socioeconomic status
SF-36	Short Form 36
UCRIHS	University Committee on Research Involving Human Subjects

Chapter 1

1 Introduction

In the hierarchy of Epidemiological studies clinical trials are considered the 'gold standard' of all study designs. When conducted carefully with close attention to detail, with sound methodology and appropriate statistical analysis, the findings from trials are accurate to the extent possible in an experimental study, evaluating a new intervention against no, or standard intervention for the problem in question. Clinical trials have a long history and have evolved over centuries from crude 'experiments' of the past into the well-designed, standardized trials of today. Despite being crude, these experiments nevertheless laid the foundation for an epidemiologic study design that is now considered the standard methodology for comparison of competing intervention in the management of clinical pathologic conditions.

While the terms like 'trial' and 'experiment' were often used by the researchers who conducted these trials, the term 'clinical trial' was not formally defined until recent past. Meinert (1986) defined a clinical trial as "a planned experiment designed to assess the efficacy of a treatment in humans by comparing outcomes in a group of patients treated with a test treatment with those observed in a comparable group of patients receiving a control treatment, where patients in both groups are enrolled, treated, and followed over the same time period" (1). Spilker (1991) defines clinical trials as "a subset of clinical studies that evaluate investigational medicines in phase I, II and III, the clinical studies being a class of all scientific approaches to evaluate the effectiveness of

a treatment" (2). Piantadosi (1997) defines a clinical trial simply as "an experiment testing medical treatment in human subjects" (3). The definition provided by Spilker is narrow in the sense that it restricts the use of this term to trials conducted during the stages of development of a new drug, as usually seen in pharmaco-epidemiologic studies often conducted by pharmaceutical companies. Treatment or management of a disease however, often involves modalities other than drugs that before becoming accepted as standard treatment method need to be evaluated like any new drug. These other non-medicinal modalities are evaluated for their efficacy in standard epidemiological studies, namely clinical trials, just like new drugs. More recent definitions of clinical trials that encompass drugs and also non-drug treatment modalities are offered by the Dictionary of Epidemiology, and by National Institutes of Health (NIH) at its official clinical trials related website, 'clinicaltrials.gov'. The Dictionary of Epidemiology defines clinical trials as "A research activity that involves the administration of a test regimen to humans to evaluate its efficacy and safety..." (4). The use of term 'test regimen' instead of drug allows for the application of the term clinical trials to trials of all kinds not just drug trials. NIH and its clinical trials website give the following definition of a clinical trial, "A clinical trial (also clinical research) is a research study in human volunteers to answer specific health questions", it further states "carefully conducted clinical trials are the fastest and safest way to find treatments that work in people and ways to improve health. Interventional trials determine whether experimental treatments or new ways of using known therapies are safe and effective under controlled

environments" (5). The 'treatment' or 'intervention' under evaluation therefore can be anything such as a vaccine, a diagnostic test, a behavioral intervention or something as simple as education.

Depending on the main focus or objective of the trial, the NIH classifies clinical trials into several different categories. *Treatment trials* test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy. *Prevention trials* look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes. *Diagnostic trials* are conducted to find better tests or procedures for diagnosing a particular disease or condition. *Screening trials* test the best way to detect certain diseases or health conditions. *Quality of Life trials* (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness (6). What is common among all these different kinds of trials is the 'comparison' of a test intervention (drug, test, behavioral or educational intervention etc), with either no intervention or the existing standard of treatment for the disease of interest. The purpose therefore is to find, evaluate and later on implement new interventions that will improve upon what exists as contemporary standard.

Clinical trials evaluating new drugs are conducted in different phases. The trials at each phase have a different purpose and help scientists answer different questions: In Phase I trials, researchers test an experimental drug or treatment in a small group of healthy people usually no more than 20 to 80, for the first time to

evaluate its safety, determine a safe dosage range, and identify side effects. The protocols for phase I studies are more flexible and less detailed than for the subsequent phases. These studies also provide necessary information needed for designing the scientifically phase II studies.

Phase II trials, are the first controlled clinical studies of the drug and involve more subjects than phase I study but usually no more than a few hundred (100-300 subjects). The primary objectives of phase II studies are to evaluate the effectiveness of the drug based on clinical endpoints for a particular condition and to determine the dosing ranges and dose/s for phase III studies. These trials also provide information on common short-term side effects and associated risks. Some experts further differentiate this phase into phase IIA (studies to evaluate dose) and phase IIB (studies to determine effectiveness of the drug).

In Phase III trials, the experimental study drug or treatment is given to large groups of subjects several hundred to a few thousand to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely. It also provides the basis for physician labeling of the drug. Phase III trials are performed only after the preliminary evidence regarding the effectiveness of the drug has been demonstrated.

The Phase IV trials further elucidate the incidence of adverse reactions and determine the effect of the drug on morbidity and mortality (7-9). Clinical trials involving non-medicinal interventions, particularly when given as an adjunct to standard treatment are evaluated in settings similar to phase II and III trials.

The low risks (if any) posed by non-medicinal interventions such as behavioral interventions, make it unnecessary to evaluate these interventions in phase I like settings.

1.1 Development of Medical Therapeutics

Since ancient times man has experimented with herbs and oils and the like for the treatment of disease and illness. The development of 'new' oils, poultices and concoctions rested upon the judgment and reckoning of the healer and had little – if anything – to do with the comparison of one treatment against another. The surviving records from ancient times particularly Egypt and Babylon show that although there was an elaborate pharmacopoeia the therapy was irrational or ritualistic. Medicine in that era was closely allied to religion and much of the treatment was aimed at the exorcism of hostile powers. This exorcism was however, often combined with the use of poultices, purgatives and enemas (10).

Modern medicine is said to have begun in Greece with Hippocrates the father of modern medicine. The Hippocratic or Coan School that formed around him was of enormous importance in separating medicine from superstition and philosophic speculation. The studies of natural history of disease from Coan School give rich accounts of diagnosis and prognosis, but there was less success in therapeutics. While surgical treatment, particularly that of minor problems was well developed; the medical therapeutics was dominated by a priori theories. These theories however, were much less speculative than those

of the contemporary schools of thought. The Coan School provided the foundations and placed medicine on a scientific plane based on objective observation and critical deductive reasoning, and urged physicians to inquire into the best treatment (11). There is however, no evidence to suggest that experimental trials and judgment based on the results of treatment were used.

In the Middle Ages after the fall of Roman Empire, the scientific trend in European medicine was arrested. Advances in medicine and therapeutics were then made by Arabs for a brief period, as accounted in Zakaria Razi's (860-932) (better know in the west as Rhazes) book *Al-Hawi* (12). The first suggestions of rules for testing drugs are found in the encyclopedic writings of Ibn-e-Sina's (980-1037) (better known in the west as Avicenna) 'Qanoon Fi Al Tib'. He suggests that in the trial of a remedy it should be given in its natural state upon uncomplicated disease, that two opposed cases be observed, and that study be made of the time of action and the reproducibility of the effects. He further states, "The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man" (13).

Arguably the oldest recorded account of an event that comes close to the definition of a "comparative study" comes from Old Testament in the Book of Daniel (14).

1. In the third year of the reign of Jeohiakim king of Judah came Nebuchadnezzar king of Babylon unto Jerusalem, and besieged it...

3. And the king spoke unto Ashpenaz his chief officer, that he should bring in certain of the children of Israel, and of the seed royal, and of the nobles...

5. And the king appointed for them a daily portion of the king's food. And of the wine which he drank that they should be nourished for three years...

8. But Daniel proposed in his heart that he would not defile himself with the king's food, nor with the wine which he drank; therefore he requested of the chiefs of the officers that he might not defile himself...

10. And, the chief of the officers said unto Daniel: "I fear my Lord the king, who has appointed your food and drink; for why should he see your faces sad in comparison with the youths of your own age?"...

11. Then Daniel said to the steward...

12. Try they servants, I beseech thee, ten days; and let them give us pulse to eat and water to drink...

13. Then let our countenances be looked upon before thee, and the countenances of the youth that eat of the king's food...

14. So, he hearkened unto them and tried them into in this manner, and tried them for ten days...

15. And at the end of ten days their countenances appeared fairer and they were fatter in the flesh, than all the youths that did eat of the king's food.

While the events in these verses fall short of qualifying as a comparative study as it was not an intentional administration of two different diets for the purpose of studying their outcomes, it does point towards one important aspect of clinical trials – gaining knowledge of the effects of exposure by observing the outcome. Another example of acquiring information through observation can be

seen in the first expedition of the East India Company to India in the 17th century. Four ships of the company were part of this expedition and on only one of them, that of General James Lancaster, was lemon juice provided to the crew. Of the four ships only this ship remained almost totally free of scurvy, while the crew of the other three ships was badly affected by the disease. The medical men of the time did not take up this lead, but the East India Company supplied lemon juice to all its ships in subsequent expeditions. It was not until more than a century later that the treatment of scurvy with fruits containing vitamin C was evaluated in a comparative trial.

The earliest documented comparative study comprising two or more treatments of a disease was performed by James Lind (1716-1794). Lind was appalled by the death due to scurvy of three quarters of the crew, during Admiral (then commodore) Anson's circumnavigation of the world from 1740-1744. Lind planned a comparative trial of the most promising 'cures' of scurvy of the time (15). Lind writes;

"On 20th of May, 1747, I took twelve patients in the scurvy, on board the *Salisbury* at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet in common to all, *viz.*, water-gruel sweetened with sugar in the morning; fresh mutton-broth often times for dinner; at other times puddings, boiled biscuit with sugar etc.; and for supper, barley and raisins, rice and currants, sago and wine, or the like. Two of these were ordered each a quart of

cider a day. Two others took twenty-five gutts of *elixir vitriol* three times a day, upon empty stomach; using a gargle strongly acidulated with for their mouths. Two others took spoonfuls of vinegar three times a day, upon an empty stomach; having their gruels and their other food well acidulated with it, as also the gargle for their mouth. The two worst patients, with the tendons in the ham rigid (a symptom none other had), were put under a course of seawater. Of this, they drank half a pint every day, and sometimes more or less as it operated, by way of a gentle physic. Two others had each two oranges and one lemon given them everyday. These they ate with greediness, at different times, upon empty stomach. They continued but six days under this course, having consumed the quantity that could be spared. The two remaining patients took the bigness of a nutmeg three times a day, of an electuary recommended by a hospital surgeon, made of garlic, mustard-seed, *rad. raphan*, balsam of Peru, and gum myrrh; using common drink, barley water well acidulated with tamarinds; by a decoction of which. With the addition of *cremor tartar*, they were gently purged three or four time during the course.

The consequence was, that the most sudden and visible effects were perceived from the use of the oranges and lemons; one of those who had taken them, being at the end of six days fit for duty. The spots were not indeed at that time quite off his body, nor his gums sound; but without any other medicine, than a gargarism of *elixir vitriol.* He became quite healthy before we came in Plymouth, which was on the 16th of June. The other was the best recovered of

any in his condition; and being now seemed pretty well, was appointed nurse to the rest of the sick."

Lind's experiment was indeed a conscious attempt to compare several treatments. His allusion to "..cases were as similar..", suggests that he was aware of the dangers of comparison between non similar cases.

While Lind's experiment was the trials of treatments, the earliest documented account of a trial of preventive nature comes from the 18th century. Eighteenth century Ottomans practiced a form of vaccination against small pox, referred to as variolation. It involved taking material such as pus from pustules in patients with mild disease and introducing this material into healthy individuals through nose or skin. This practice was based on observation that patients who survived smallpox remained immune to it for the rest of their life. An English aristocrat, Lady Mary Montague (a smallpox victim), the wife of the English ambassador to the Ottoman government became interested in the Turks' variolation process and is said to be responsible for bringing variolation to England. She and the English embassy surgeon Charles Maitland persuaded King George I to allow a 'trial' of variolation on six convicts in 1721. All six convicts survived and were released as promised (16). This trial was later criticized as it was unclear which of the subjects had previously suffered from disease, and the trial would have tested the safety of variolation (or inoculation) rather than its effectiveness (17).

Another example of the use of comparative statistics is the report by Robert Robertson in 1776. While serving as ship surgeon on Juno, of the Royal

Navy, Robertson ran out of the bark that was then commonly employed for the treatment of continuous fever (malaria), and was forced to try other methods of treatment, thus leading to an un-intentional comparative study. Robertson then compared the case fatality percentages in the two periods (with and without bark), and reported these rates in his report (10, 18).

Such comparative studies continued into the nineteenth century. The comparison of statistics such as fatality percentages became more and more refined, in parallel with the developments in statistics. The hygienic and sanitary reform movement of the 19th century, utilized vital statistics as a justification for proposed reforms, as they provided a quantitative measure of the community's health status. The work of Louis René Villermé, who compared the mortality experience of different districts in Paris, and that of William Farr are excellent examples (19); Wall, 1974 #288}.

One of the best examples of strength of observational epidemiology with some degree of random assignment (though unintentional) comes from the work of John Snow, during the London's cholera epidemics of 1849, and 1853 (20). A change in the water supply of London, in the period between epidemics gave Snow the opportunity to do what he referred to as the 'grand experiment'. Of the three companies that supplied the city with its drinking water at that time, one (Lambeth) moved its source of water intake to upstream Thames, from an area that was much less polluted than the uptake areas of other companies. While Snow's contemporaries favored miasmatic theory, as the cause of cholera, this unique arrangement of water supply, enabled Snow to demonstrate that the

households differed considerably in terms of mortality (and incidence) of cholera also differed by their source of drinking water. Since these households were in the same neighborhood, even in the same street, the difference in water source as an explanation of very different observed mortality rates made good sense. These differences couldn't be explained by the miasmatic theory. The 'randomness' with which households differed in their source of water supply, and the ability to compare the disease pattern before and after the change in water supply are important of modern day clinical trials.

Perhaps the most sophisticated clinical trial of the preventive type in the nineteenth century was conducted by Ignaz Sammelweis. Sammelweis observed that mortality in the First Division of Lying-in hospital Vienna, served by physicians and medical students, was much higher than the Second Division, served by midwives, he also noted that because of the stress on learning Pathology medical students and physicians were in much frequent contact with cadavers, whereas the midwives had none. Sammelweis hypothesized that "..cadaveric particles clinging on to the hands are not entirely removed by the ordinary method of washing hands with soap,..". In May 1847 he began the use of 'chlorina liquida'. Each student in the First Division was required to wash his hands with this before examining a patient. This resulted in an immediate drop in the mortality rates in the First Division to a level similar to Second Division. Although not randomized and without a placebo, the trial did show a strong preventive effect of using antiseptics in preventing infection (21).

Similar statistical comparisons can be found in the work of researchers in the 19th century. In 1860 Joseph Lister used comparative statistics to evaluate the effects of antiseptics on the mortality from amputations. Using hospital records, he compared two years of data prior to the 'antiseptic period' with the three years during the antiseptic use. Despite small numbers, which he acknowledged, he was able to show much lower mortality following amputation in the antiseptic period as compared to previous years (22). While statistical comparisons mentioned above made use of a group without 'intervention' the use of the term 'control' was probably first used by Hankin in 1890, when he used the term 'control-mice' to describe untreated mice in a series of experiments of tetanus immunization.

As the researchers continued to conduct 'trials' the strength of careful observation and information gained from it became apparent to the scientific world. This continuous evolutionary process resulted in refinement of design and conduct as the trial moved from the primitive comparisons of the 19th century into the modern day trials of the 21st century. Advancement in statistics also played a major role in this process with more and more statistical tools applied to the later trials.

Although researchers had alluded to the concept of randomization or random assignment even earlier, the first clear application of the concept was seen in agricultural experiments designed by RA Fisher, in 1926. Working at Rothamsted Experimental Station in England, he used random allocation of agricultural fields to different treatments. The first formal random assignment of

patients in a clinical trial was done by Amberson, in his trials of Sanocrysin (a gold compound) for the treatment of pulmonary tuberculosis. Amberson is also credited for introducing the concept of a double blind design for the same trial. This was achieved by giving intravenous injections of distilled water to the controls. Diehl et al. reported the first use of a 'saline placebo' in their trials of cold vaccine trials, in 1938.

While researchers perfected their study designs by introducing new techniques, lawmakers realizing the potential benefits of a well-designed and conducted trial, started enacting laws and regulation to ensure quality control (and ethical acceptability) of the clinical trials. Starting with Pure Food and Drug Act in 1906 the first regulations were laid out for regulation of clinical trials. A brief timeline of such regulations are given in the appendix 1.

The historical account and the evolution of the regulations governing clinical trials, as given in appendix 1 highlight the fact that clinical trials have not only evolved over time, from primitive comparisons to sophisticated randomized trial of today, but that their evolution is a continuous ongoing process. Being very different from research in disciplines like Physics and Chemistry, epidemiological research – in most cases – deals with human subjects and thus has limits on the extent to which one can probe into the subjects and subject matter. These restrictions imply that 'perfection' in study designs and methodology is virtually unattainable and that there will always be room for improvement even in the best conceived and conducted trials.

1.2 Attrition in Clinical trials

One of the limitations of clinical trials, and of all follow-up study designs involving humans, is the subject attrition or the loss to follow-up. This loss of participants represents a potentially large threat to validity of the trial results. This loss can be completely random, where dropout subjects cannot be assumed to belong to a group based on any of their characteristics, i.e. the dropout is independent of the patients' assigned treatment, given observed characteristics. If this is indeed the case then patient loss of such kind will not result in drawing of invalid conclusions (other than by chance), however the reduction in available sample for analysis will reduce the power of the study to detect a significant effect when there was indeed an effect of the intervention on the outcome. Potential losses and drawback of non-significant findings due to lack of statistical power are several and include; delay in obtaining convincing evidence of the effect of an intervention on an outcome, as well as wasting of valuable, and increasingly scarce, resources. This reduction in the power of the study, or increase in the probability of the type II error, can occur despite the traditional '10 – 20% inflation' of the calculated sample size, if a substantial percentage of the sample is lost.

The non-random (or disease directed) loss on the other hand can result in serious bias and inaccurate conclusions in addition to the loss of statistical power. In a clinical trial, for example, if exposed patients are indeed more likely to develop disease and at the same time, with the development of disease, more likely to drop out of the study, the final sample may be under-representative of

exposed cases, and thus may result in failure to recognize the exposure's association with disease, or in an under-estimation of the effect of exposure on disease at the minimum. This can work in opposite direction as well resulting in an over-estimation of the magnitude of association between exposure and disease. This missing data resulting from patients attrition poses particular serious challenges to the accurate assessment of all clinical trial data, including cancer-related QOL (23-25).

Strictly speaking refusal to participate in a trial despite eligibility cannot be considered attrition, but this non-consent tends to impact the study results as does attrition after randomization. Both scenarios represent subject loss and can potentially have an impact on the validity of trial's results. Non-consent can lead to the 'healthy participant effect', in which participants report more healthy life styles or lower risk factors than the non-participants, as underscored by several studies (26-28). It is also generally recognized that patient attrition after enrollment can potentially introduce bias in the study and make the results unreliable (29). Biases originating from differential patterns of attrition from different study groups after enrollment can result in, under or over estimation of the magnitude of the effect of intervention or exposure, on the outcome of interest.

Research to identify factors that distinguish study subjects who participate in the study till its end, from those who do not participate till the end, (dropouts) can play a role in improving the quality of trials. Addressing this research

question will require an analysis comparing study completers vs. non-completers of a trial.

Comparison of study completers with those who consent to participate but do not complete the study may be very difficult, if not impossible. This will depend on the point in time when the attrition occurred. If some patients dropped out soon after consent was obtained but before any formal data collection, like baseline or intake interview was done, the unavailability of the extensive relevant data will make meaningful comparisons very difficult. Some information such as that may have been collected at the time of recruitment, or that may have been collected from patients' medical chart records can be used to make comparisons of study completers and those early dropouts. On the other hand when attrition occurs at a later point in time, i.e. after patients have at least completed a baseline or intake interview, the comparison of completers vs. non-completers of the study is relatively easy. Such analysis can prove extremely advantageous in revealing factors that have an association with a high probability of dropping out of the study, and their identification can help researchers in better understanding the extent of potential bias introduced in a given study. Additionally a before hand knowledge of such factors when designing a study can help researchers build checks into the study design, targeting patients at high risk of dropping out to at least minimize their attrition. Researchers of trials and other follow-up studies have traditionally limited their assessment of the attrition to a simple univariate analysis of the comparison of 'lost' vs. 'retained' subjects in an attempt to show that statistically the completers of the study were not significantly

different from the subjects lost, in terms of their demographic and sometimes other characteristics (30).

1.3 Literature on Attrition

Though the problem of patient attrition from clinical trials and its potential impact on the study results were discussed as early as 1962, by Lasky (31), and more recently by Leon (32), there is relatively scarce literature on research/analysis done specifically to look for the independent effect of participant characteristics on their probability of attrition from the study. Additionally, the research that has been carried out has identified a somewhat variable set of predictors of attrition, with very few factors being reported with any consistency. Socio-demographic factors such as old age, being male, low socioeconomic status (SES), low education, low social support and belonging to minority groups have been found to be associated with patients' attrition (33-36). Physical and mental factors associated with attrition include, functional limitations, poor self-reported health, unstable health status, cognitive impairment and major disease (36-38). In addition, other studies have reported females, smokers, and depressed individuals to be more likely to drop out than others (39-41). Younger age, milder disease symptoms and fewer coexisting chronic conditions have also been reported to be associated with patients' attrition (42-45). Patient depression is one factor that is perhaps most consistently reported factor to be associated with attrition (44, 46, 47). An early work published by Downing et al, found that younger and gainfully employed patients, those with a lower socio-economic status and social stability were more likely to be non-

completers of placebo-controlled trials (48). Demographic characteristics such as belonging to a minority group, not being married and having low education (less than 12 years) were reported by Given et al (49). The wide variation of characteristics reported in literature, suggests that factors influencing a person's chances of attrition may vary by the type of disease (if any) the participants may have, and point to the need for further exploration of factors affecting patients' attrition. While there can be several sources of these variations, it is intuitive that source population would be one major cause of this variation. The nature of disease (if any), that the patients are suffering from and/or kind of intervention they may be undergoing may, in itself be a cause of attrition. In a study by Davis et al, the researchers looked at the characteristics of two groups of caregivers of elderly patients, suffering from Alzheimer's and Parkinson's diseases, who dropped out of intervention trials. They showed that the nature of disease influenced the caregivers' attrition (50). An interesting research into factors associated with attrition comes from Medical Research Council Cognitive Function and Aging Study (MRC CFAS). MRC CFAS is a population-based study of health in older population, carried out in England. The researchers in their recent article (51), report that factors associated with patient attrition over a ten year period were fairly consistent, with, patients of low socio-economic status, lower education and older patients with poor cognitive function to be more likely to drop out before the formal termination of study. Snow et al, studying attrition in a clinical trial of lung cancer patients, report that patients who were younger, unmarried and smoked cigarette were more likely to drop out. They

also looked if the mechanism of recruitment of study participants had an impact on attrition or not and found that patients recruited via mass mailing, were more likely to stay in the study till its end than those recruited through worksite or referral methods (52). An additional source of attrition from behavioral interventions trials is the random assignment of patient to an intervention other than the patients' choice. The resulting disinterest is an obvious cause of attrition (53). The contrasting associations of age with attrition, reported in literature, may very well be a function of the age range of participants of a given study. It is plausible that the two ends of the age spectrum, very young and very old may be the ones most or least vulnerable to attrition, with mid-age range representing either a more stable or labile group in terms of continuous participation. Thus depending on the age range of participants in any given trial, the researchers may find, and report, older or younger patients to be more likely to dropout. All this points to the need of more research to gain a better understanding of factors associated with patients' attrition.

The research reported here was conducted in two very different populations, enrolled in two different non-drug clinical trials, one of relatively younger, cardiac patients, and the other of cancer patients undergoing chemotherapy. Data from both trials was analyzed separately, to identify disease and intervention specific factors associated with patients' attrition. Both trials collected data via telephone interviews, at baseline (soon after recruitment) and on at least two more occasions following baseline. This analysis was carried out on patients who had completed at least the first (baseline) interview.

The objective of this research was to identify patient and disease related factors that influence participants' chances of dropping out from clinical trials of cognitive behavioral interventions.

Chapter 2

2 Methods

The data sources for this analysis are two multi-site clinical trials, "Heart After-Hospital Recovery Planner" (HARP), and "Family Home Care for Cancer (FHCC) – A Community Based Model". HARP is a clinical trial involving cardiac patients, whereas FHCC is a cancer care intervention involving cancer patients and their primary family caregivers. Both studies were conducted by researchers at Michigan State University (MSU) with data collected from multiple sites and were person-level randomized non-drug intervention trials.

2.1 Ethical Concerns

Since the data in the original trials was collected via interviews on human subjects, both trials were conducted after Institutional Review Board (IRB) approval from MSU's University Committee on Research Involving Human Subjects (UCRIHS). Separate IRB approvals were also obtained for this research.

2.2 HARP Trial

Patients recruited for the HARP intervention, and randomized into the intervention arm, received a follow-up telephone coaching program during the first three months following discharge from the hospital. The institutional review boards of Michigan State University and each of the five participating hospitals approved the study. HARP study was designed to target multiple risk behaviors

of cardiac patients, with an aim of improving overall quality of life of cardiac patients and mortality following discharge from hospital.

2.2.1 Subjects and settings for HARP study

Patient eligibility criteria included: admission to one of five participating study hospitals in mid-Michigan, a documented serum Troponin I level greater than the upper limits of normal observed in each hospital, a working diagnosis of acute coronary syndrome (ACS), and capability of being interviewed and/or participating in telephone health behavior counseling. Exclusion criteria included: discharge to any non-home setting, possession of any significant mental/cognitive impairments, lack of a home telephone, or non-English speaking.

Between January 14, 2002 and April 13, 2003, trained nurse recruiters approached ACS patients during their hospitalization, providing information on study participation and attempted to obtain their consent to participate. Patients were recruited from five hospitals located in two communities in adjacent mid-Michigan counties. Both counties shared similar characteristics. Each had one major city surrounded by suburbs and outlying rural and farming areas. Both communities have diverse populations with a minority population slightly higher than the State average (20% versus 14.5%), high unemployment rates (above 8%), and with an industrial/manufacturing economic base, dominated by a single automobile manufacturing corporation as the largest employer. A mean number of 2.29 (SD 1.82) contacts were required with elevated Troponin patients to determine their actual eligibility.

Of the 1985 eligible patients, 719 consented to participate in the study. Shortly after hospital discharge consenting patients were called by trained survey researchers from MSU's Institute for Public Policy and Social Research (IPPSR), for a 30-40 minute interview to collect the first wave (Baseline) data. IPPSR researchers made up to three attempts to contact and interview the patients. Patients not contacted in the three attempts or who explicitly refused interview were not contacted any further.

Five hundred and twenty five (73%) of the 719 consenting patients were successfully contacted and interviewed at baseline. Telephone calls were repeated at approximately 3 months and 8 months following discharge, to collect follow-up data. Of the 525 patients participating in baseline interview, 440 (84%) were successfully contacted and interviewed at the first follow-up contact and 388 patients (74% of the 525 patients who completed baseline interview and 88.2% of the 440 who participated in first follow-up interview) were successfully contacted and interviewed at the second follow-up contact (Figure 1).

2.2.2 HARP Intervention

Patients in the HARP Intervention arm received a six-session health behavior change program, over a six week period, within the first three months following discharge from hospital, delivered via telephone by a trained health educator or "coach". The primary health behavior goal focus of the program included: (1) the reduction or quit smoking, (2) an increase in physical activity, and (3) an improved healthy diet. The program adapted a relapse prevention smoking cessation program model for use with the multiple risk behaviors of

cardiac patients (54). Although smoking patients were encouraged to consider smoking cessation as a first priority, they were also encouraged to be openly expressive about setting risk factor reduction goals they were actually prepared to implement.

Coaching telephone sessions averaged 15 to 30 minutes. Behavior change processes included behavioral staging, motivational interviewing, goal setting, relapse prevention, and social support. Patients were encouraged to identify at least one current behavior they intended to improve upon and set weekly goal(s) in that selected behavioral area(s). Each patient and his/her family had received a 25-page booklet and goal worksheets that provided information related to the major health goal behaviors to consider during program sessions. Goal setting within the intervention group is described in detail elsewhere (55).

2.2.3 Study Variables and data collection

The outcome of interest in this analysis was patients' attrition. For each interview session, a patient was classified as 'attrited' if he/she did no complete the next scheduled interview. Therefore patients who completed baseline and the first follow-up interview, but not the last interview, were coded as '0' (not attrited) at the baseline interview but as '1' (attrited) at the first follow-up. Similarly patients who completed baseline interview only were coded '0' at baseline since baseline was the first and the last point in time when data could be available from them. Patients who completed all three interviews were coded '0' (not attrited) for both, the baseline and the first follow-up interview (Appendix

2). In this manner were able to determine outcome at baseline and first follow-up interview, and thus analysis included all patients who complete first follow-up and/or baseline interview.

Of the primary interest in this analysis were the variables on patients' demographics, severity of illness, medications and measures of quality of life. The main measure for the severity of patient's disease was left ventricular ejection fraction (LVEF). Ejection fraction was obtained from the chart review and dichotomized into two categories, LVEF > 35% and EF ≤ 35%. This cutoff value has important prognostic implications in heart disease (56-58). Another measure used was Charlson Comorbidity Index (CCI) (59). Coexisting morbidities (not the index ACS) were counted in calculating the CCI weighted score. In our analysis this variable was evaluated as continuous and then categorized as a three level variable: 0 to 1 (few or no co-morbidities), 2-3 (moderate level of co-morbidity), or ≥ 4 (severe level of co-morbidity).

The main source of data on medication prescriptions was patient's medical chart. The data from medical charts was abstracted using a structured questionnaire by trained nurse abstracters. All medicines were classified as prescribed as before the index hospitalization (patient reporting being on a prescription before the cardiac event), those that were prescribed during the hospital stay and those that were prescribed at the time of discharge form hospital. Obviously some medicines were prescribed at more than once instance, for example, during hospital stay and also at discharge.

Also of interest were patients' health behaviors of physical activity, diet, steps taken to lose weight (if overweight) and smoking habits. Smoking status at the time of hospitalization was established based on two sources of information: the medical record chart audits, which contained an entry about current and past smoking behavior, and the baseline interview. Respondents who reported that they quitted smoking were asked how long ago that was. Comparing the time between the baseline interview and the original hospital admission, we could establish who quitted recently, but was still a smoker at the time of hospitalization. In the subsequent 3-month and 8-month interviews, smoking status (current (continuing) smoker, relapsed, previous and new quitter) was reassessed.

Patients' overall functional status was measured by the Activity Status Index (ASI) (60), which provides a weighted composite score computed from answers to questions about 12 activities of daily living of progressive intensity. Scale scores for the ASI range from 0 to 58.2 points, with a higher composite score indicating greater functional capacity. The ASI has been shown to be highly correlated with oxygen uptake on treadmill exercise, and has been widely used as an outcome in ACS (60). Prior research has demonstrated that ASI has adequate sensitivity to show clinical changes in physical function for cardiac patients (61, 62). The ASI was evaluated at baseline (assessed functional status before the onset of disease), and at both the follow-up interviews.

In the interviews patients' depression status was evaluated using the Center for Epidemiologic Studies (CES-D) Depression scale. CES-D is a 20-item

self-report screening instrument designed to measure the relative frequency of the occurrence of several depression symptoms within non-psychiatric community populations. Each item response is scored on an ordinal scale of 0 to 3, with a possible range of the summated composite scale scores from 0 (no depressive symptoms) to 60 (highest level of symptoms). A composite CES-D score of 16 or greater is generally considered an indicator of at least mild depression symptoms (63). In this analysis, the CES-D scores for all patients were categorized into two groups. Those with CES-D scores of 16 or higher were classified as "depressed" and those below 16 were classified as "not-depressed". This cutoff is consistent with that used in contemporary literature and corresponds to 80th percentile scores for community samples and has a 95% sensitivity for diagnosing depression among low-income women (64, 65).

Additional quality of life measures such as EuroQol (66) and Quality of Life after Myocardial infarction (QLMI) (67) were also evaluated. All measures that can vary over time, such as ASI, CESD, QLMI, EuroQol etc. were re-evaluated at the two follow-up interviews.

Mortality of patients in the study was obtained from a family member's report when the patient was called for an interview. This information was supplemented by mortality data, which were obtained from the Michigan department of Vital Statistics.

2.3 Family Home Care for Cancer Trial

2.3.1 Subjects and Settings for FHCC Trial

The family home care for caner trial focused on the care of cancer patients at home, therefore inclusion criteria required that each otherwise eligible patients should have a recognized family member who was the primary caregiver at home for the patient. Dyads, patient and caregiver, instead of just patient were recruited for the study. For participation in this study the patients had to be 21 years of age or older, be within 57 days of initiating a first course of chemotherapy, and have a designated family caregiver, 21 years of age or older, who also agreed to participate in the study. Once potential participants were identified, the project was explained to the dyad, and upon agreeing to participate, both members of the dyad signed consent forms. Following a baseline interview, dyads were randomized to one of the two study arms; 1) conventional care alone or 2) conventional care plus a 10-contact, 20-week nurse-directed intervention. Subsequent interviews for both dyads in the control and experimental arms occurred at 10 weeks (after the conclusion of the 4^{th} intervention contact), at about 20 weeks (after completing the intervention), and at about 32 weeks to assess the effect of the intervention. The medical records of all patients were reviewed at about 32 weeks after the baseline interview to verify diagnosis and treatment information, as well as to track patients' access of the health care system (office visits and visits to the emergency room).

Of the 609 patients found eligible on screening and approached by recruiters, 263 (43.2%) dyads (patients and their caregivers) agreed to participate in the study and signed the consent form. Three hundred and forty six (56.8% of 609) dyads refused participation citing a variety of reasons, common among them were being too ill, not interested, too busy, already participating in another study, feeling overwhelmed, or not wanting to be randomly assigned as part of their participation and a variety of other personal reasons. In this dissertation any patient who skipped an interview was considered to have dropped out at that contact and from future contacts, if any. Therefore, of the 263 patients, 235 (89.4%) completed the first (baseline) interview. Of the 235 patients who completed the baseline interview, 178 (75.7%) completed the first follow-up interview. One hundred and Thirty Nine or 78.1% of those who completed the second follow-up and of them 125 (89.9%) completed the last follow-up interview. For this analysis therefore, we were able to code the outcome (attrition) at baseline and first and second follow-up contacts. Thus the final multiple record file for analysis contained a total of 552 records, representing 235 baseline interviews, and 178 and 139, first and second follow-up contacts respectively (Figure 2).

2.3.2 The nursing intervention

All patients randomized to the intervention arm were given a 10-contact, 20-week intervention in addition to conventional care. A nurse who specialized in cancer care directed the intervention. The main aim of the intervention was to assist patients and their caregivers with symptom monitoring and management,

education, emotional support, and coordination of services. At each visit, the nurse intervener used a customized computer program to assess symptom status, functional level, communication and the emotional health (anxiety & depressive symptoms) of the patients. Assessment required the patients to rate both the intensity of the symptom and the impact of the symptom on their quality of life as well as appetite, normal daily activities, emotions/mood, and sleep. Whenever a symptom had a high intensity or reached the threshold on the impact score, the computer program automatically posted the symptom to the patient's plan of care. Following the assessment, the nurse intervener and patient reviewed the problems and mutually choose those problems that the patient would work on over the upcoming weeks (next contact). Once problems were chosen, the nurse intervener used the customized computer program to generate interventions aimed at decreasing the intensity or impact of the problem. Subsequent visits involved the evaluation of patients' ability to implement suggested interventions, as well as their ability in communicating care needs to, and enlisting assistance in meeting care needs from, their caregivers. A more detailed description of intervention and its effect on reducing symptom severity can be found elsewhere (68, 69).

2.3.3 Study variables

As in the cardiac patients trial the main outcome of interest in the cancer intervention trial was patients' attrition, and was defined in exactly the same manner as described above (Appendix 3). The only difference being that, since

4 interviews (1 baseline, three follow-ups) were conducted for this study, we were able to determine the attrition status at three time intervals.

The covariates of interest included demographic factors such as patient's age, sex, race, education, marital status (social support) etc. Education was recorded as a seven-category variable, ranging from 'no formal education' to 'gradate or professional degree'. In this analysis, because some categories had very few observations, we collapsed few categories to make education a four category variable 'less than high school', 'high school', 'more than high school to completed college' and 'more than college'. An evaluation of this new variable's association with attrition in a regression model revealed that patients with 'less than high school' education stood out differently from all the three other groups, in terms of attrition, and the other three groups were not different from each other. This variable was therefore converted to a two-level variable, consisting of 'less than high school' and 'high school and above' groups. Marital status recorded as a 4 level variable, was also recoded as a two level variable 'married' and 'unmarried'. Patients' race for analytic purposes was recoded as a binary variable (whites and minorities) as reported earlier for the cardiac patients study.

Disease related factors were also of interest such as stage of cancer and site of cancer. Patients with cancers of seven different sites were recruited in the original study. However, because there were relatively few patients with certain cancers, this variable was recoded into 'lung cancer' and 'other cancers' categories. Summary measures of variables related to patients' symptoms, were also assessed for possible association with chances of patients dropping out of

the study. These measures included, total number of symptoms experienced at each interview, total severity of symptoms, total limitation of daily activity caused by symptoms, total bother felt by patient due to the symptoms. Symptom severity was recorded on a 10-Point scale for each symptom, with '0' indicting absence of symptom (zero severity) and '10' representing worst possible severity. The total symptom severity reflects sum of the reported severities over all individual symptoms.

The Short Form 36 (SF-36) health survey tool was used to measure health status of patients (70). SF-36 is a multi-purpose, short-form health survey made up of 36 questions. It yields an 8-Point-scale profile of functional health and well-being scores covering both physical as well as mental health. It is a generic measure, non-age, disease, or treatment specific. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments (71-73). In this study the 10-Point physical function sub-scale of SF-36 was used.

Other quality of life measures such as depression (CES-D) and total optimism score were also evaluated for possible impact on attrition. Depression was measured and used in the same manner as described earlier (binary, with categories as <16 and ≥ 16). Patients' employment status, treatment procedures, hospitalization for chemotherapy, surgery, radiation etc. were also evaluated.

2.4 Statistical Analysis

Data from the two studies were organized separately into two multiple record files. The HARP data had either one or two records (observations) per patient, depending upon whether that patient completed only the baseline interview or at least baseline and the first follow-up interview. All patients completing first follow-up interview had their outcome coded as either '0' (non-attrited) if they also completed the second follow-up interview, or as '1', if first follow-up was the last interview they completed. In the FHCC data, the outcome variable coding process was similar to HARP data, except that maximum number of records contributed by patients was 3 instead of 2.

Both data sets were modeled using the Generalized Estimating Equation (GEE) method (66, 74, 75) using SAS version 9.0 (SAS software, SAS institute). The GEE represents a class of models that are often utilized for analyzing data that are correlated. The method can be used for both linear as well as categorical outcomes. As in the general linear model (GLM), a function of the mean $g(\mu)$, where g is called the link function, is modeled as a linear function in the regression parameters. For a dichotomous outcome (as in our study) the 'logit' link is commonly used. Thus the $g(\mu)$ equals logit (P), where P is the conditional probability of Y=1 (the patient had attrition) given the values of all covariate, define a the vector X. If there are p independent variables, this can be expressed as; logit $P(Y=1 \mid X)$ equals β_o plus the summation of the product terms for the p independent variables times their beta coefficients. In the equation form

this can be written as logit $P[y=1 \mid x] = \beta_0 + \beta_1 X_1 + ... + \beta_k X_k$. This equation is presented with acknowledgement that GEE estimates additional correlation parameters that work in the background and are not explicitly stated in the equation. The GEE model for dichotomous outcome data thus looks similar to the standard logistic model, except it incorporates the correlation between repeated outcomes from the same patient. A particular covariance structure is assumed and employed by the GEE model for estimation of the model parameters. In addition, the standard logistic models use likelihood estimation function as their estimation method, but the GEE method follow quasi-likelihood estimation method (76).

To accommodate the correlated nature of the outcome variable, the GEE analysis of correlated data (like data presented in this analysis, with multiple observations or records per person), requires specification of correlation structure by the user. The correlated nature of the outcome variable can easily be summarized by drawing a correlation matrix of observations made on an individual patient at different points in time. A separate correlation matrix would be needed for each stratum (person) in the study, which would require estimation of a very large number of parameters. If, however, there are more parameters to be estimated than the total number of observations in the data set, the model is over-parameterized, and does not yield valid estimates. To avoid this problem, the GEE requires that each subject have a common set of correlation parameters. This substantially reduces the number of correlation parameters. Although the GEE requires specification of correlation structure by the user, the

advantage of the GEE is that even if the correlation structure is incorrectly specified the obtained parameter estimates are consistent. The variance of the parameter estimate is however affected. The GEE yields two sets of variance estimators: 1) the model-based estimators and 2) the empirical (robust) estimators. The model-based estimators are similar to the maximum likelihood based general linear model (GLM) variance estimators, and although the likelihood for GEE is never formulated, the parameter estimates are consistent if correlation structure is correctly specified. The empirical variance estimators represent an adjustment of model-based estimators. While both approaches make use of the specified correlation structure, the empirical estimators also take into account the observed correlation between responses in the data. The use of empirical estimators is advantageous as they are consistent even if the correlation structure is incorrectly specified. This, however, does not mean that when empirical estimators are used the correct specification of the correlation matrix becomes redundant. The correct specification (choosing one close to real correlation) results in gaining efficiency. This is particularly true if the number or clusters (patients in our case) is large, meaning that incorrect specification will result in unreliable results if the number of clusters is small (76).

In our data set we specified exchangeable correlation structure, and the odds ratios and their confidence intervals are reported making use of empirical (robust) estimators. The exchangeable correlation structure assumes that any two within subject outcome responses in different time points have the same correlation.

For model building, all variables in the two data sets (if present) that were cited in literature to be associated with patients' attrition and all that could have a plausible association with patient's chances of attrition from the trials were initially evaluated in a univariate model (one independent variable at a time) to assess their unadjusted effect on the outcome. This served as a guide for selecting variables for evaluation in a multivariate model. All variables having a p-value of 0.2 or less were candidates for further evaluation; additionally any variables that we considered to be biologically important were assessed even if they did not meet the p-value cutoff criterion. Model building was carried out in the manner generally recommended by standard textbooks (76, 77). The variable found most significant in the univariate analysis was entered into the model followed by the next most significant variable. The impact on the model, of the addition of new variable was evaluated by change in the score test statistic. This continued until all candidate variables were evaluated and the impact of their addition or deletion on the model was assessed. The final model represents a parsimonious model with variables that impact the score statistic significantly, and where addition of further new variables does not bring a significant change in the model. A few variables, as mentioned earlier, were kept in the model despite their insignificant impact, because of their biological importance. The score statistic was also used to evaluate the overall significance of the model, evaluating all the variables simultaneously. The purpose of multivariate modeling was to estimate the independent effect of

factors (variables) on patients' chance of attrition. The details of this univariate analysis are presented in table 3 (HARP data) and table 5 (FHCC data).

Chapter 3

3 Results

Since the analysis presented here was performed on two different datasets that came from fairly different patient populations in terms of their morbidity, it is presented under separate subheadings.

3.1 HARP Trial

Participants' progress through the study is described in figure 1. Approximately a quarter of patients were lost between baseline interview and the last (8 month) follow-up interview. Following the baseline interview all patients were randomly assigned to either the intervention (n=268) or control group (n=257). Tables 1 and 2 summarize the comparison of the intervention and control groups, displaying comparability of the two groups. As stated earlier all plausible variables in the data set were first evaluated in the univariate models to identify candidates for evaluation in the multivariate model. Table 3 shows the results of this univariate analysis for selected variables. At the univariate level, patients' smoking status, education (less than high school vs. High school and more), Race (Minorities vs. whites), marital status (unmarried vs. married), depression status (CESD $\geq$ 16 vs. $<$ 16), alcohol consumption (consumers vs. abstainers) and better quality of life as measured by EQ5, attained significance at the level of significance of 0.05. However, all variables attaining a p-value of 0.2 or less were candidates for evaluation in the multivariate model. Following the univariate analysis, the process of multivariate modeling was completed and the

final model resulting from this exercise is described here. Because of the longitudinal nature of the data the time variable (representing the time of interview) was included among covariates in the model even though it did not reach statistical significance. Additionally the group variable (that identified patients' group assignment as intervention or control), and the variable identifying patients who died during the study period were also included in the final model. Thus the effects reported from this multivariate model are adjusted for patients' group assignment, death and the time of attrition. Death was retained in the model to identify and estimate the effects of the factors affecting patients' attrition above and beyond that is caused by mortality.

Age of the patient plays an important role in attrition among the cardiac patients. A detailed study of the effect of age over time, that included several higher order terms, reveals a non-linear, quadratic 'U' shaped relationship between patients' age and attrition (Age coefficient, -0.2130, 95% CI of coefficient -0.3124, -0.1136, Age Squared, coefficient, 0.0017, 95% CI of coefficient 0.0009, 0.0025). This means that estimation of the effect of a person's age on his or her probability of attrition form the trial requires two and not one coefficient. In other words, the probability of attrition of a 40 years old patient as compared to a 30 years old patient is not same as the probability of attrition of a 30 years old patient as compared to a 20 years old patient, despite the fact that the difference in both cases is the same, i.e. 10 years.

Patients' self-reported smoking status was also a strong predictor of attrition. This was a four category variable as described earlier. As compared

with non-smokers the smokers, recent quitters and past smokers, all were more likely to drop out. The respective adjusted odds ratios and their 95% confidence intervals (CI) were: smokers (AOR 2.65, 95% CI 1.27-5.51), recent quitters (AOR 2.90, 95% CI 1.41-5.98) and past quitters (AOR 2.04, 95% CI 0.94-4.41). The past smokers although having a high odds ratio were not significantly different from non-smokers in terms of attrition. Also smokers were not found to be different from recent quitters in terms of attrition. Patients with a CES-D score of 16 or higher (Indicative of clinical depression) were found to be more likely to drop out of the study than those with a CES-D score of less than16 (AOR 1.62, 95% C.I. 1.10 – 2.39). Patients who reported alcohol consumption as compared to complete abstainers were found to be less likely to drop out from the study (AOR 0.53, 95% C.I. 0.35 – 0.81). In other words the adjusted odds ratio for abstainers relative to those who reported alcohol consumption was 1.88, 95% CI 1.23 – 2.86. These results are summarized in table 4. As stated earlier, a large number of variables were tested at univariate level for modeling purposes. The final model reported above was based on variables that were of biological importance and that reached statistical significance. The detailed univariate analysis is presented in table 3.

3.2 FHCC TRIAL

Participants' progress in FHCC study's different stages is described in figure 2. Almost half of the patients were lost between the baseline and the third follow-up interviews. Following the baseline interview all patients were randomly assigned to an intervention (n = 117) or a control (n = 118) arm. Tables 5 & 6

summarize the comparison of the intervention and control groups in terms of various demographic and clinical characteristics, and show no significant differences between the two arms of the trial. The approach and methodology for analysis of patient's attrition for the FHCC was similar to the approach employed for the HARP trial. All plausible variables were assessed in the univariate (one variable at a time) models and the selected candidate variables were evaluated to develop the final multivariate model. Table 7, displays the result of the univariate analysis of selected variables. In the univariate analysis patients' sex (male vs. female), site of cancer (lung vs. others), time of interview (baseline, second, third), education, anxiety, depression (CESD $\geq$ 16 vs. $<$ 16) and hospitalization for chemotherapy were found to be statistically significant at 5% level. However, as in the cardiac patients' data a cutoff of p-value $\leq$ 0.2 was used to qualify variables for further consideration and evaluation in the multivariate model.

Table 8, summarizes the final multivariate GEE model identifying factors associated with attrition in cancer patients. As in the previous data set, the model described here was adjusted for mortality and patients study group assignment. We found that lung cancer patients were more likely to drop out of the trial than patients with other cancers (AOR 2.13, 95% CI 1.28-3.53). Consistent with the finding in the HARP data depressed patients (CESD $\geq$ 16) were more likely to drop out than non-depressed (AOR 1.73, 95% CI 1.03-2.91). Education was found to be a strong predictor of attrition. Patients with less than high school education were more likely to drop out than those who had

completed at least the high school (AOR 7.53, 95% CI 2.27-24.97). The time (Wave) variable identifying each data collection wave was retained in the model because of the longitudinal nature of the study, the odds ratios for wave1 and 2 were higher as compared to wave 3 (AOR 2.19, 95% CI 1.04-4.66, and 2.87, 1.37-5.98 respectively).

Chapter 4

4 Discussion

Realizing that patients' attrition from clinical trials can have its origin in several different areas such as patients' personal characteristics, or the disease patients are suffering from, or the type and nature of interventions tested in the trial, we set out to evaluate all the available information in the studies analyzed, that fell into one of these areas. Conceptually, we focused our analysis on evaluation of factors from the three areas mentioned, such as patients' age, gender, education, employment status, race etc. Similarly, within each study, disease related factors, such as severity of the disease were also evaluated. We also looked at the patients' compliance or non-compliance with intervention expectations, such as quitting smoking in cardiac patients' trial.

Despite data coming from two different clinical trials and having two very different diseases, there were similarities in many respects. The majority of patients were recruited from similar, if not the same, geographical areas in mid-Michigan. The two sets of patients were very similar in their age distribution, with mean age of cardiac patients being 59.78 (SD 12.00) years, and that of cancer patients being 59.72 (SD 10.34) years. Caucasian whites made up the majority of patients in both data sets (90% for FHCC, 85% for HARP). The differences found in the factors associated with patients' attrition in the two studies could therefore largely be attributed to the differences in the nature of diseases patients had or differences in the two interventions.

Age of the patient, among cardiac patients, plays an important and complex role in their attrition from clinical trials, displaying a 'U' shaped effect with maximum attrition at the two extremes of the age distribution. Attrition was high in the youngest patients but declines until middle age but then climbs with increasing age. The probability of patients' dropping out of the study was the lowest at age 63 and after that it started rising again. To illustrate this with an example with two arbitrarily chosen patients of ages 53 and 73 years respectively (10 years younger and 10 years older than the group with lowest probability of attrition i.e. 63 years), their respective adjusted odds ratios as compared to a 63 years old patient after adjusting for the variable in the model are 1.17 and 1.20 respectively, highlighting that both the younger and older patients are more likely to drop out than 63 years old patients. Younger age, better health, and higher percentage of employed patients, as may be expected at the middle age, explain why attrition may be higher among younger patients. On the other hand, higher attrition in older patients is also not surprising, as the older patients are likely to be unhealthier, with higher existing co-morbidities, be more fragile and more likely to be repeatedly hospitalized or moved into a nursing home. Our data show a significant positive correlation between patients' number of co-morbidities and age ($p<0.001$), as well as between age and employment. Employed patients were on average more than 11 years younger than unemployed ones ($p<0.001$). Both these findings help explain higher attrition among older patients and are consistent with the non-linear relationship of age with patient attrition. A significant association with patient age was not detected in FHCC data. The

FHCC data had a narrower age range as compared to HARP data (51 years Vs. 69 years), and the oldest patient in the FHCC trial was 87 years old, as compared with a 100 year old patient in the HARP trial. The narrow age range and fewer very old patients could be the reason for not finding an effect of age on attrition. However, the fragility and other conditions associated with old age are well recognized and for this reason patients age was retained in statistical model despite not reaching the statistical significance. Finding a statistically significant effect of age in HARP but not in FHCC could also be due to the difference in the sample sizes of the two studies. FHCC trial had a smaller sample size than HARP, and therefore an inability to find a significant effect could be due to insufficient power to find such a difference.

Social isolation and seclusion play a role in attrition as seen, by greater likelihood of depressed patients to dropout of the study, in both trials. We found that depressed patients were more likely to drop out than non-depressed (cardiac patients AOR 1.62, 95% CI 1.10 – 2.39, and cancer patients AOR 1.73, 95% CI 1.03 – 2.91). We also found that in the HARP Trial, unmarried patients were more likely to drop out than married patients in the univariate analysis. Similarly among cancer patients, those who scored higher on the anxiety scale were more likely to drop out than those scoring lower on the anxiety scale. Since depression and anxiety (78-80), and depression and marital status (81-83) are associated with each other, after addition of depression to the model either variable did not add any new information and were thus removed from the final model. The association of social activity (or the lack of it) was further highlighted

by our finding that cardiac patients who reported complete alcohol abstinence were more likely to drop out than those who considered themselves alcohol drinkers. Since people are more likely to consume alcohol during social events, complete abstinence could be an indicator of no or at least minimal social participation which can explain attrition from the study (84).

Diseases, that are chronic and "incurable" tend to have a depressing effect on those suffering from them, and if these patients also lack social support, they tend to go into seclusion and usually diminish or cutoff contact with the rest of the world. In contemporary literature, depression is perhaps the most consistently reported factor associated with attrition from research studies (44, 47). Social isolation and seclusion associated with depression can explain the higher attrition observed in depressed patients as compared to non-depressed patients. Depressed patient with coronary artery disease also have higher mortality than non-depressed cardiac patients (85), though mortality was lower in the cardiac patients' study. Studies have also shown that depressed patients are also less likely to follow caregivers' advice regarding the management of their co-existing health conditions (86). In behavioral intervention trials, like the ones reported here, requiring behavioral changes, depression may also mediate attrition by this mechanism.

There are a few reports, in the literature, indicating a higher attrition among smokers as compared to non-smokers (87), as also seen in the cardiac patients study reported here. All cardiac patients, who are smokers, are advised smoking cessation by their care providers, on top of that the intervention in the

HARP study particularly emphasized on patients smoking habits, encouraging smokers to quit smoking. Patients who fail to comply with their health care provider's advice, may feel social pressure, and choose to drop out of he study rather than participating and remaining in the study. Similarly it has been shown that in behavioral studies patients who fail to achieve the desired study goal tend to drop out of the study before its completion (88). We found that patients who continued to smoke and those who reported quitting recently (in most cases after their cardiac event), were more likely to drop out than non-smokers. Patients who reported quitting smoking recently, may not have completely overcome their habit, making them more similar to smokers than non-smokers and thus were more likely to drop out (like smokers) than non-smokers. The past smokers (those who quitted more than 1 year prior to the interview) represent a more health conscious group that gave up smoking on their own or on their health providers advice before their cardiac event, and because of an initiative on their own, rather than their adverse event, were more successful in kicking their habit and were more similar to non-smokers, and thus not different from non-smokers in terms of attrition.

More aggressive nature of disease (lung cancer in cancer patients' case) was also found to increase the likelihood of attrition. A more severe and aggressive disease is obviously associated with higher mortality, which would lead to higher attrition. More aggressive and severe disease is also associated with higher morbidity, which can also lead to frequent hospital visits/admissions, and even admission to hospice. This would explain finding an independent effect

of more aggressive disease (lung cancer) over and above that caused by mortality.

We found that among the cancer patients, education played a role in attrition. As described earlier the effect of education was initially evaluated in four categories, but three categories were collapsed into one, to dichotomize this variable into, those with less than high school education, and those with high or higher level of education. Less educated patients were more likely to drop out than those that were better educated. This finding is consistent with similar reports by other researchers (42, 45, 87, 89, 90). Inability to fully understand and appreciate the value of research and participation in clinical studies, likely because of non-exposure to research and its advantages by patients' lower level of education, explain why they may be more likely to drop out than better educated patients (91). A similar effect of lower level of education on attrition was also found in the univariate analysis of cardiac patients' data (OR 1.6486, 95% CI 1.0485 – 2.5923). Smoking habits have an association with education, with low educated people more likely to smoke than better educated, which was also seen in our data ($p = 0.04$), and thus could be the reason for failure of education to add information to our model in the presence of smoking status. We also found that attrition of patients decreased with passage of time. This means patients who were to drop out tended to drop out early. This was an effect observed in both, cardiac as well as cancer patients, but reached statistical significance only among cancer patients. Given that disease aggressiveness and severity was one factor responsible for attrition of patients, it is plausible that

such patients, being more severely ill, would drop out earlier than later. Disease severity (as measured by left ventricular ejection fraction) did not play as strong a role in attrition in cardiac patients, as in cancer patients; which could explain why the time of attrition did not reach statistical significance with cardiac patients. Additionally the two studies differed in the number of follow-ups, and the intervals between the follow-ups that could also contribute to significance or non-significance.

Specification of a correlation structure in longitudinal analysis using GEE is not always easy. In our studies where the outcome variable was of non-recurring nature this was particularly difficult. In our studies the way the outcome variable was defined, meant that until the interview wave where attrition occurred outcome variable at previous time intervals were perfectly correlated. We reviewed the correlation matrix and found our assumption of exchangeable correlation for modeling to be reasonable. Additionally, a major advantage of GEE is that even if the correlation structure is incorrectly specified the obtained parameter estimates are consistent. Therefore despite the unique nature of our outcome variable we believe our parameter estimate to be reasonably valid.

4.1 Conclusion

Starting with the youngest cardiac patients, attrition from longitudinal studies declines with increasing age, though in a non-linear manner. With further increase in age the declining effect becomes less and less pronounced, and then probably because of general ill health, and more co-morbidities starts climbing

again among the oldest patients, however in populations with diseases associated with higher morbidity and terminal illness, such a cancer, other psychosocial and demographic factors play a stronger role in determining patients' continuation (or attrition) from clinical trials. Social support and interactions play an important role in determining patients' attrition from research studies. Social isolation increases and social activity and social interactions decrease a patient's likelihood of attrition. Depressed patients are also more likely to drop out of the clinical trials. Presence of depression has its own effect in addition to that it exerts through social isolation and seclusion. Other factors such as aggressive and severe disease also make the patients drop out from the studies.

To the best of our knowledge our study is the first of its kind to evaluate factors associated with patients' attrition using longitudinal models. Since such models take into account the variation within observation (study subjects) and also take into account the changing nature of time-varying characteristics, the models used here are more appropriate in identifying characteristics that can otherwise be missed by other statistical techniques.

It is not possible to 'intervene' to eliminate many factors that promote attrition, but using the profiles described here, researchers carrying out clinical trials can identify participants that are at higher risk of dropping out of the study. With a priori idea of who is more likely to drop out during the course of the trial and who is not the researchers should attempt to build mechanisms into their studies aimed specifically at high-risk patients to at least minimize their attrition.

Common sense strategies such as proper training of interview data collectors and other study personnel who come in contact with study subjects, better communication with subjects, expression of appreciation of patients' participation and time etc are recommended by experts (92). Involvement of family members can help address the factors like depression and seclusion, which would translate not only into improved retention of patients in the trials but will also have a beneficial effect on the quality of life of the patients. The identification of somewhat different set of predictors of attrition, in groups of patients with different diseases, point to a need for studies to be carried out in patients with other chronic conditions as well.

Clinical trials are usually designed to answer a specific research question or a set of research questions that most often relate to evaluation of an intervention – pharmaceutical or otherwise. Therefore the data from these trials often lacks information on factors and characteristics that may be important from the point of view of studying attrition. A trial conducted solely to study attrition experience and patterns of participants, without any other research question, will of course be illogical, or even meaningless. However, when conducting trials for evaluation of a new treatment modality the researchers should consider collecting, in addition to what is required for the primary purpose of the trial, information on factors identified in contemporary literature as associated with attrition, as well as factors that may intuitively be considered worth evaluating for possible association with attrition.

Such research has the potential of further improving quality of clinical trials, resulting in improvement of the validity of the findings from such trials.

Table 1: Comparison of baseline demographic characteristics of the intervention and control groups of the HARP trial (categorical variables)

Variable	Intervention n=268 n(%)	Control n=257 n(%)	p-value
Gender			
Male	173 (64.6)	161 (62.6)	0.65
Female	95 (35.4)	96 (37.4)	
Marital Status			
Married	183 (68.3)	167 (65.2)	0.51
Unmarried	85 (31.7)	90 (34.8)	
Race			
Non-Hispanic white	228 (85.1)	215 (83.7)	0.50
African American	32 (11.9)	28 (10.9)	
Hispanic white	5 (1.9)	7 (2.7)	
American Indian	3 (1.1)	7 (2.7)	
Smoking status			
Never smoked	82 (30.6)	92 (35.8)	0.32
Quit > 1 year ago	90 (33.6)	89 (34.6)	
Quit ≤ 1 year ago	67 (25.0)	48 (18.7)	
Current smoker	29 (10.8)	28 (10.9)	
Alcohol Drinking			
Yes	202 (75.4)	201 (78.2)	0.47
No	66 (24.6)	56 (21.8)	

Table 2: Comparison of baseline demographic characteristics of the intervention and control groups of HARP Trial (continuous variables)

Variable	Intervention	Control	p-value
Age	58.9	60.5	0.13
Years of education	13.12	13.25	0.84
Household Income (in $)	36,585	42,774	0.16
SF-36 General Health Scale	3.18	3.30	0.24
Beck's Hopelessness score	7.75	7.93	0.11
QLMI – Symptoms subscale	5.10	5.13	0.77
QLMI - Confidence subscale	5.21	5.24	0.73
QLMI - Self-esteem subscale	5.99	5.93	0.55
EurQol	0.75	0.74	0.55
ASI	29.12	30.00	0.55
CES-D	14.00	13.09	0.32

Table 3. Factors associated with patient's attrition based on univariate analysis (HARP Trial)

Variable	Odds Ratio	95% CI
Age	0.99	0.98 – 1.01
Sex (Ref: Males)		
Females	1.28	0.88 – 1.86
Smoking Status (Ref: Non-Smokers)		
Current smoker	2.78	1.32 – 5.88
Recent quitter	2.58	1.21 – 5.48
Past smoker	2.14	0.97 – 4.70
Education (Ref = High School and above)		
< High School	1.66	1.06 –2.58
Race (Ref: Non-Hispanic Whites)		
Minorities	1.69	1.05 – 2.70
Marital Status (Ref: Married)		
Unmarried	1.84	1.26 – 2.68
Employment Status (Ref: Employed)		
Unemployed	1.03	0.71 – 1.49
Depression Status (Ref: CESD < 16)		
CESD ≥ 16	1.74	1.19 – 2.54
Alcohol consumption (Ref: Consumers)		
Abstainers	1.78	1.18 – 2.68
Left Ventricular Ejection Fraction (Ref: ≥ 35)		
< 35	1.14	0.74 – 1.76

Table 3 (Continued): Factors associated with patient's attrition based on univariate analysis (HARP Trial)

Variable	Odds Ratio	95% Confidence Interval of Odds ratio
Coronary Artery Bypass Graft (CABG)	0.84	0.55 – 1.30
Angioplasty	0.86	0.29 – 2.52
Angioplasty + CABG	0.55	0.12 – 1.51
EuroQol Score (EQ5)	1.69	1.05 – 2.70
QLMI Symptoms subscale	0.86	0.74 – 1.00
QLMI Self-Esteem subscale	0.88	0.76 – 1.02
QLMI Confidence subscale	0.78	0.65 – 0.94
Activity Status Index	1.01	0.99 – 1.02
Co-morbidities (Charlson's weighted index)	1.08	0.93 – 1.25

Table 4: Factors associated with post-baseline attrition in cardiac patient's based on the final Multivariate GEE model, (n = 525)

Variable	Odds Ratio	95% Confidence Interval for Odds Ratio	p-value (Type III)
Age[1]	-0.2130[1]	-0.3124, -0.1136[1]	<0.01
Age Squared[1]	0.0017[1]	0.0009, 0.0025[1]	<0.01
Smoking Status			
Current smoker	2.65	1.27 - 5.51	
Recent quitter	2.90	1.41 - 5.98	<0.01
Past smoker	2.04	0.94 - 4.41	
Depression score (CESD)			
≥ 16	1.62	1.10 - 2.39	0.01
Drink alcohol	0.53	0.35 - 0.81	<0.01

Model adjusted for patient's death, time of interview and patient's group assignment.

[1]Parameter estimates and their respective 95% confidence intervals, instead of odds ratios are reported for variables age and age squared.

Table 5: Comparison of baseline demographic characteristics of the intervention and control groups in the FHCC trial (categorical variables)

Variable	Intervention n=117 n(%)	Control n=118 n(%)	p-value
Gender			
Male	32 (27.35)	31 (26.27)	0.85
Female	85 (72.65)	87 (73.73)	
Marital Status			
Married	29 (24.79)	32 (27.35)	0.65
Unmarried	88 (75.21)	85 (72.65)	
Race			
Non-Hispanic white	106 (90.60)	107 (90.68)	0.98
Minorities	11 (9.40)	11 (9.32)	
Education			
< High School	4 (3.42)	11 (9.32)	0.17
High School	28 (23.93)	27 (22.88)	
> high School to College	59 (50.43)	48 (40.68)	
More than college	26 (22.22)	32 (27.12)	

Table 5 (Continued): Comparison of baseline demographic characteristics of the intervention and control groups in the FHCC trial (categorical variables)

Variable	Intervention n=117 n(%)	Control n=118 n(%)	p-value
Cancer Site			
Breast	47 (40.17)	46 (38.98)	
Colon	13 (11.11)	13 (11.02)	
Gynecological	12 (10.26)	12 (10.17)	
Lung	40 (34.19)	41 (34.75)	0.98
Lymphoma	4 (3.42)	4 (3.39)	
Pancreatic	1 (0.85)	1 (0.85)	
Other	0 (0.0)	1 (0.85)	
Lung Cancer			
Yes	77 (65.81)	77 (65.25)	0.92
No	40 (34.19)	41 (34.75)	
Stage of cancer			
Early	40 (34.48)	37 (32.17)	0.71
Late	76 (65.52)	78 (67.83)	

Table 6: Comparison of baseline demographic characteristics of the intervention and control groups in the FHCC trial (continuous variables)

Variable	Intervention Mean (SD)	Control Mean (SD)	p-value
Age	60.50 (9.80)	58.94 (10.82)	0.25
Total Symptoms	5.42 (3.39)	5.42 (3.08)	0.99
Total Symptom Severity	28.91 (20.04)	26.86 (19.68)	0.44
Total Symptoms Limitation	23.14 (19.84)	20.52 (19.64)	0.32
Total Symptoms Bother	26.36 (21.07)	23.79 (20.93)	0.36
Total Mastery of Care	25.39 (4.84)	25.07 (4.72)	0.62
SF-36 Physical Function	63.55 (29.53)	64.21 (27.65)	0.86
SF-36 Physical Role Impact	28.92 (37.69)	29.13 (37.42)	0.97
SF-36 Emotional Role Impact	62.96 (40.54)	65.24 (40.33)	0.67
SF-36 Bodily Pain	61.97 (29.14)	64.89 (26.89)	0.43
SF-36 General Health	53.55 (24.33)	54.28 (25.60)	0.83
SF-36 Vitality	50.34 (22.93)	49.83 (24.10)	0.87
SF-36 Social Functioning	59.40 (31.09)	60.79 (31.14)	0.73
SF-36 Mental Health	73.81 (19.64)	75.17 (17.99)	0.58
Total Optimism	24.92 (3.76)	25.32 (4.41)	0.63
Total Anxiety Score	33.77 (11.60)	36.63 (13.14)	0.08
CES-D	12.19 (9.05)	13.62 (9.05)	0.24
Total Procedures Performed	1.44 (1.57)	1.42 (1.57)	0.90
Total Complications	4.08 (3.15)	3.97 (3.59)	0.80

Table 7: Factors associated with patient's attrition based on univariate analysis (FHCC Trial)

Variable	Odds Ratio	95% CI for OR	p-Value (type III)
Age	1.01	0.99 - 1.03	0.24
Sex (male)	2.10	1.29 - 3.41	0.004
Stage of Cancer	0.62	0.38 - 1.02	0.053
Lung cancer	0.46	0.30 - 0.73	0.001
Interview waves (Ref = Wave3)			
Wave1	2.79	1.49 - 5.24	0.002
Wave2	2.50	1.30 - 4.83	
Education (Ref = College and above)			
< High School	4.06	1.53 - 10.76	0.014
High School	0.91	0.49 - 1.69	
More than high school to College	0.72	0.41 - 1.27	
Race (Ref: Non-Hispanic Whites)			
Minorities	0.82	0.37 - 1.81	0.61
Marital Status (Ref: Married)			
Unmarried	0.82	0.49 – 1.35	0.42
Patient's Mastery	0.97	0.92 - 1.02	0.22
SF-36 (Physical well-being)	0.998	0.990 - 1.005	0.62
SF-36 (Absence of body pain)	1.003	0.99 - 1.01	0.46
SF-36 (Lack of physical role impact)	0.998	0.993 - 1.004	0.67

Table 7 (Continued): Factors associated with patient's attrition based on univariate analysis (FHCC Trial)

Variable	Odds Ratio	95% CI for Odds Ratio	p-Value (type III)
SF-36 (Lack of Emotional role impact)	0.997	0.992 - 1.002	0.28
SF-36 (General health)	0.996	0.987 - 1.005	0.46
SF-36 (Vitality)	0.993	0.984 - 1.003	0.17
SF-36 (Social Functioning)	0.997	0.991 - 1.004	0.45
SF-36 (Mental health)	0.994	0.983 - 1.01	0.35
Total Symptoms	1.06	0.99 - 1.13	0.09
Total symptom severity	1.01	0.99 - 1.02	0.082
Total limitations due to symptoms	1.008	0.99 - 1.02	0.20
Total bother due to symptoms	1.009	0.998 - 1.019	0.12
Anxiety	1.02	1.001 - 1.037	0.043
Depression (CESD)	1.03	1.008 - 1.056	0.011
CESD (>16) Ref = <= 16.	1.85	1.14 - 3.01	0.02
Gainfully employed	0.83	0.51 - 1.35	0.45
Household Income	1.005	0.99 - 1.01	0.27
Complications	1.06	0.99 - 1.12	0.070
Radiation (No)	1.17	0.75 - 1.83	0.48
Surgery (No)	1.02	0.62 - 1.66	0.94
Hospitalization for chemo	1.79	1.14 - 2.81	0.01

Table 8: Factors associated with patient's post-baseline attrition in the FHCC trial based on the final Multivariate GEE model (n = 235).

Variable	Odds Ratio	95% Confidence Limits of Odds ratio	p-value (Type 3)
Age	0.99	0.98 - 1.02	0.95
Cancer Site			
Lung Vs.Other	2.13	1.28 - 3.53	<0.01
Interview wave			
Baseline	2.19	1.04 - 4.66	<0.01
First Follow-up	2.87	1.37 - 5.98	
Depression score (CESD)			
≥ 16	1.73	1.03 - 2.91	0.04
Education			
< High School Vs. High School and more	7.53	2.27 - 24.97	<0.01

Model adjusted for patient's death, time of interview and patient's group assignment

Figure 1: Flow chart showing patient flow through various stages of cardiac patients' (HARP) Trial.

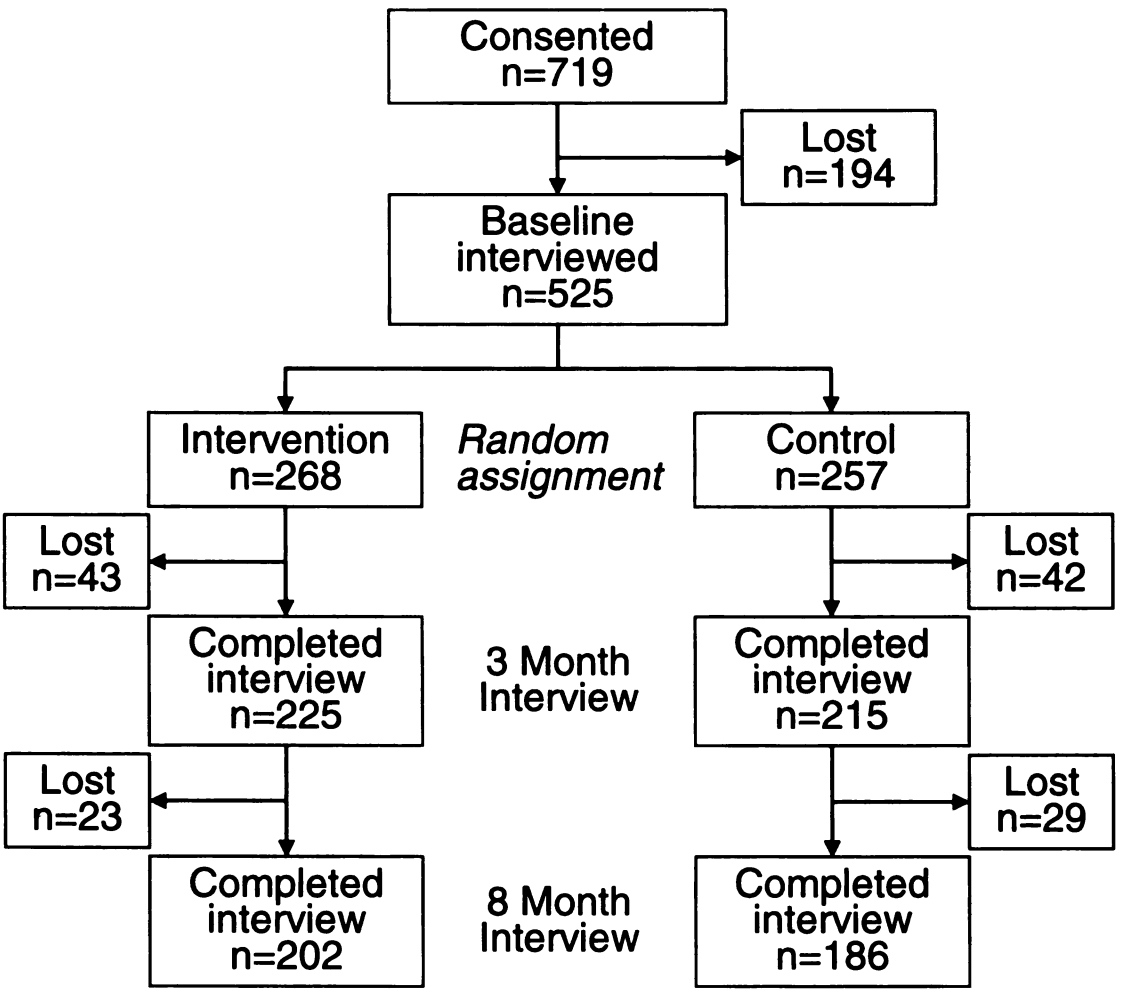
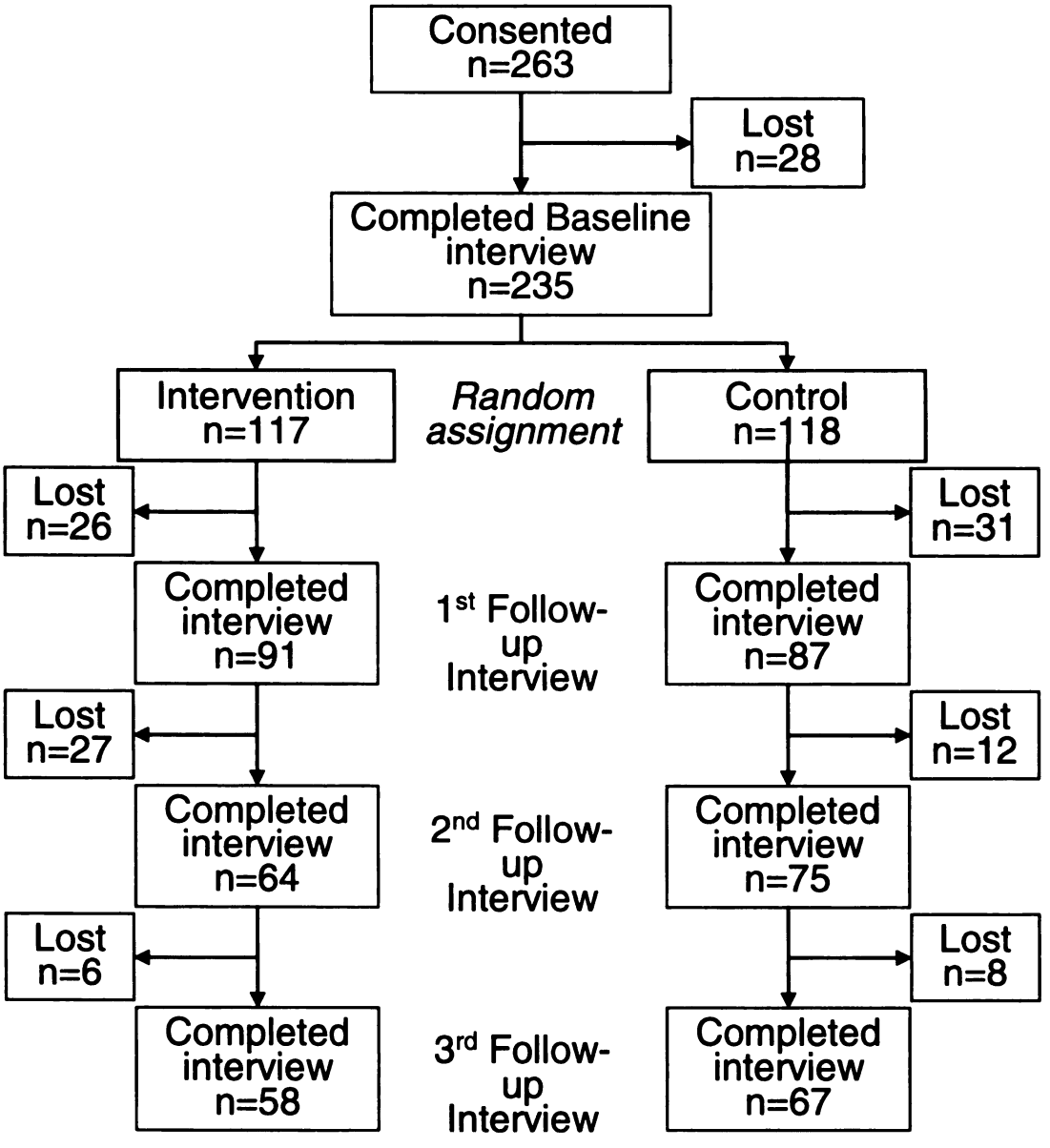


Figure 2: Flow chart showing patient flow through various stages of cancer patients' (FHCC) study.



Appendices

Appendix 1: Timeline of select important events in development of clinical trials regulations

Year	Act or regulation
1906	Pure Food and Drug Act passed
1931	Formation of U.S. Food and Drug Administration (FDA)
1938	U.S. Federal Food, Drug and Cosmetic Act
1952	Designation of drugs as prescription or over he counter (OTC) by FDA
1966	Mandated creation of Institutional Review boards (IRBs) for funding by the U.S. Public Health Service
1976	Medical Device Amendment to the U.S. Food, Drug Cosmetic Act
1977	Publication of General Considerations for Clinical Evaluation of Drugs
1985	Publication of Guidelines for the Format and Content of the Clinical and Statistical Section of an Application
1987	Treatment IND (FDA)
1992	Parallel track and accelerated approval, FDA
1997	Publication of Good Clinical Practice Consolidated Guidelines

Appendix 2: Format of the attrition (outcome) variable along with an example of fixed (gender) and time-varying (CESD) covariates in the HARP dataset

Comment	Participant #	Fixed covariates e.g. Gender	Time varying covariates e.g. CESD	Attrition[1]
Completed baseline only	1	Female	15	1
Completed two interviews only	2	Female	27	0
	2	Female	19	1
Completed all 3 interviews	3	Male	24	0
	3	Male	15	0

[1] 1 = Attrition, 0 = No attrition until next wave

Appendix 3: Format of the attrition (outcome) variable along with an example of fixed (gender) and time-varying (CESD) covariates in the FHCC dataset

Comment	Participant #	Fixed covariates e.g. Gender	Time varying covariates e.g. CESD	Attrition[1]
Completed baseline only	1	Female	15	1
Completed 2 interviews only	2	Male	24	0
	2	Male	15	1
Completed 3 interviews only	3	Female	27	0
	3	Female	19	0
	3	Female	18	1
Completed all four interviews	4	Female	42	0
	4	Female	31	0
	4	Female	33	0

[1] 1 = Attrition, 0 = No attrition until next wave

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