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Comparing the Effectiveness of Using Educational Booklet or Brief Video on Patients' Knowledge, Perceptions and Willingness to Participate in Placebo-Controlled Clinical Trials

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DISSERTATION

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Dedication

I would like to honor my much-loved mother “Muneerah AlMoaikel” and my father “Fahad AlMoaikel” by dedicating my dissertation work to them. I would not have been able to seek my doctorate without your constant support, encouragement and love. I cannot fully express in words how to thank you for all what you have given me in my whole life. This dissertation is also dedicated to my brothers and my sister and especially “Mohammed” and “Ibrahim” for their support and believing in me. Without you all, I would not have been able to complete this dissertation successfully.

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Abstract

Background and Objectives: Limited knowledge about clinical trials can influence a patient's willingness to participate in medical research. For placebo-controlled clinical trials, it is more difficult to recruit patients compared to clinical trials without a placebo arm. Thus, educating individuals about clinical trials and placebos can potentially improve their perceptions about clinical trials and might increase their willingness to enroll in them. The study objectives include:

1) To design educational interventions (a booklet and a video) to improve a patient's knowledge of placebo controlled clinical trials.

2) To compare the impact of the educational interventions (booklet, video or both) on a patient's knowledge of placebo-controlled clinical trials, perceptions (perceived benefits and perceived barriers) related to and their willingness to participate in placebo-controlled clinical trials.

Methods: Patients from 3 different clinics (N=108) were randomly assigned to one of the following groups; booklet, video, both the booklet and video and control group. A paper based questionnaire was administered to measure patient's knowledge, perception and their willingness to participate in placebo-controlled clinical trials.

Results: Patients in the booklet group had a knowledge score of 9.59 (±0.74) out of 10 possible points. Patients in the video group scored 9.66 (±0.55) and patients in the booklet and video group scored 9.66 (±0.62) points, which was slightly a higher knowledge score compared to the booklet group. Patients in the control group had the lowest knowledge score of 8.03 (±1.84) points. There was a significant statistical difference in the knowledge score among the four groups ($p< 0.01$). The educational materials used in the three interventional groups increased patient positive perceptions. There was no significant difference related to number of patients willing to participate in placebo-controlled trials among the different groups.

Conclusions: The study results showed that the educational interventions were able to increase patient knowledge about placebo-controlled clinical trials significantly compared to the control group. Moreover, the educational interventions increased patient positive perceptions related to perceived benefits and reduced perceived barriers towards placebo-controlled clinical trials. The results of this study showed that patient knowledge was not a significant predictor of patient perceived barriers, benefits or their willingness to participate in clinical trials. These findings showed that a patient knowledge is not sufficient to increase participation in placebo-controlled clinical trials and that interventions need to go beyond educating knowledge to patients.

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List of Acronyms

RCT……..Randomized Clinical Trials
FDA……..Food and Drug Administration
NCI……National Cancer Institute
CLT……..Cognitive Load Theory
HBM……..Health Belief Model
ICH……International Conference of Harmonization
RR……..Relative Risk
OR……..Odds Ratio
PAH……..Pulmonary Arterial Hypertension
ICF……..Informed Consent Form
DSMB……..Data and Safety Monitoring Committee
SA……..Strongly Agree
A……..Agree
SWA……..Somewhat Agree
D……..Disagree
SWD……..Somewhat Disagree
SD……..Strongly Disagree
ANOVA……..Analysis of Variance
VIF……Variance Inflation Factor

CHAPTER 1

INTRODUCTION

Background:

The first recorded controlled clinical trial to cure scurvy was conducted by a naval surgeon, James Lind in 1746.[1] Since that date, Randomized Controlled Clinical Trials (RCT's) are considered to be the gold standard of evidence-based medicine. Appropriately designed RCT's provide valid assessments of the safety and efficacy of treatments, diagnostics, and preventive interventions. RCT's are quantitative, comparative and controlled experiments and the most rigorous way to determine whether a cause-effect relationship exists between an intervention and outcomes. RCT's have several important features such as:[2]

- Random allocation to intervention or control groups
- Patients and investigators are blinded to the intervention and control and remain unaware of which treatment was given until the study is completed
- Intervention groups are treated identically except for the experimental treatment
- Patients are normally analyzed within the group to which they were randomized.
- The analysis is focused on estimating the size of the difference in predefined outcomes between intervention and control groups.

Other study designs, including non-randomized controlled trials, can detect associations between interventions and outcomes, but they cannot rule out the possibility that the association was caused by a third factor linked to both intervention and outcome. Random allocation ensures no systematic differences between intervention and control groups in factors, known and unknown, that may affect outcome.

An uncontrolled trial of a new drug obviously cannot rule out the possibility that effects unrelated to the biochemical mechanism of the drug, including spontaneous

remission or psychological effects, are responsible for a seemingly favorable treatment outcome, while comparisons with an established drug can not preclude the possibility that both drugs are ineffective.[3]

The purpose of a control group is to allow discrimination of the patient outcome from an outcome caused by other factors (such as natural history or observer or patient expectation) as well as to avoid bias. A control group in a clinical trial may use any of the following:

(1) Placebo

(2) No treatment

(3) Different dose or regimen of the study treatment,

(4) Different active treatment

(5) Historical control.

Placebo-Controlled Clinical Trials- Overview

Diehl and colleagues were the first to use a saline solution injection as a placebo control in their cold vaccine study in 1938.[4] For clinical researchers, placebos are essential tools in RCT's to control for bias and psychological components of healing and thus isolate the specific effect of a new drug or treatment. Placebo controlled trials are very common as the Food and Drug Administration (FDA) prefers them in the process to approve most new drugs. The recent developments in medicine allow the design of many new therapeutic agents with high molecular targeting levels. Many of these agents were tested in placebo-controlled clinical trials.[5] Table 1 shows some examples for therapeutic agents tested in placebo-controlled trials in the field of oncology.[5]

Currently and according to ClinicalTrials.gov, as of 14 December 2013, there were 9149 phase 3 placebo-controlled clinical trials registered. In the areas of diabetes, kidney diseases and oncology, there were 696, 869 and 1082 placebo-controlled trials registered, respectively. These numbers clearly show the importance of placebo controlled clinical trials in medical research. Figures 1,2 and 3 show the locations and numbers of those trials in the world.

Table 1. Some examples of cancer drugs approved by the FDA after tested in placebo-controlled clinical trials [5]

Study	Agent	Disease	Setting	Design
Goss et al	Letrozole	Breast cancer	Adjuvant	Monotherapy
Escudier et al	Sorafenib	Renal cell	Metastatic	Monotherapy
Smith et al	Celecoxib	Prostate	Increasing PSA*	Monotherapy
Beer et al	Calcitriol	Prostate	HRPC**	Add on
Sparano et al	Marimastat	Breast cancer	Metastatic post first line	Monotherapy
Berek et al	Oregovomab	Ovarian cancer	Remission consolidation	Monotherapy
Shepherd et al	Marimastat	Small cell	Metastatic post first line	Monotherapy
Gatzemeier et al	Erlotinib	Non–small cell lung	Metastatic first line	Add on
Fisher et al	Tamoxifen	Breast cancer	Adjuvant	Add on

* PSA, Prostate Specific Agent
** HRPC, Hormone-Refractory Prostate Cancer

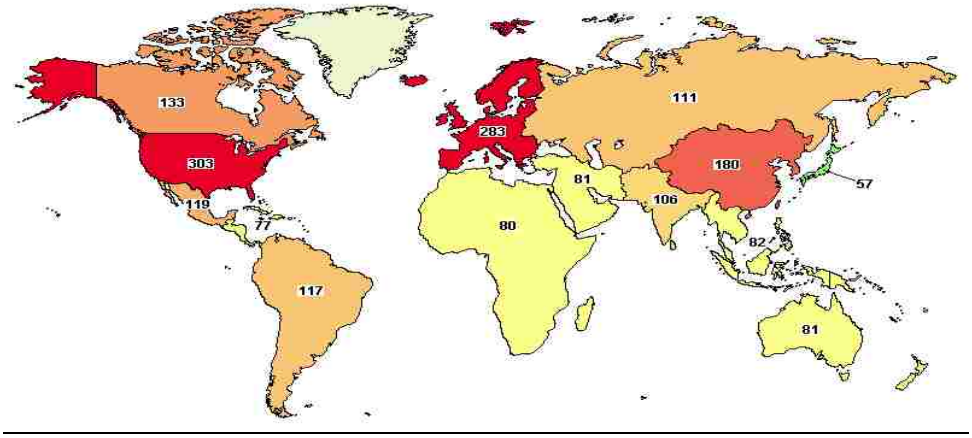


Figure 1. Locations and numbers of placebo-controlled clinical trials conducted in the field of diabetes around the world until December 2013

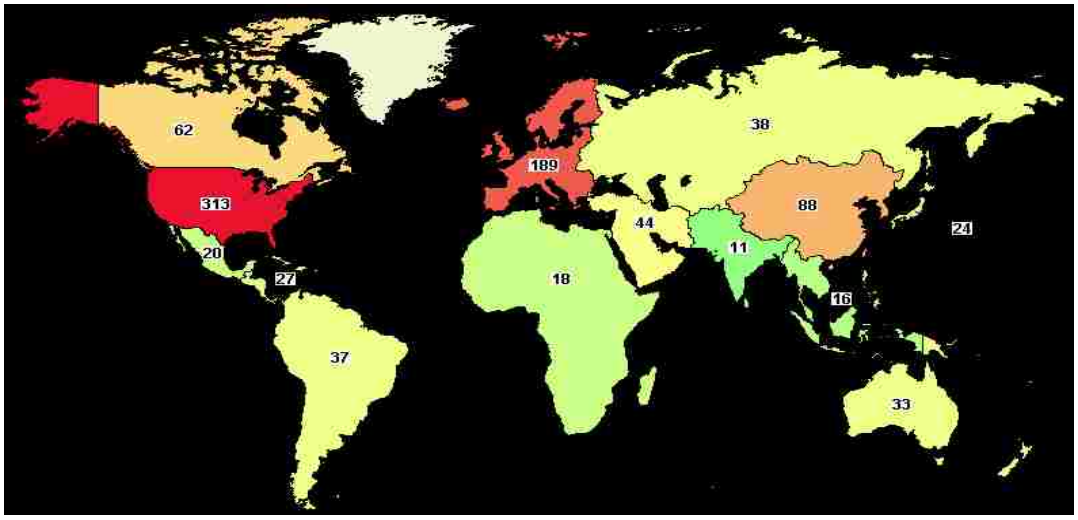


Figure 2. Locations and numbers of placebo-controlled clinical trials conducted in the field of kidney diseases around the world until December 2013

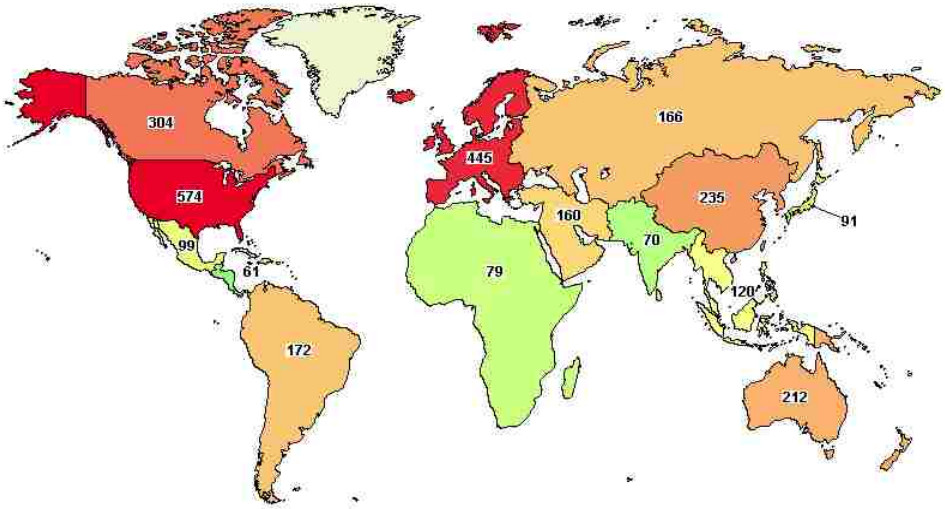


Figure 3. Locations and numbers of placebo-controlled clinical trials conducted in the field of oncology around the world until December 2013

Despite the need to use placebos in clinical trials, there are some ethical issues with their use.[6-8] One of the ethical issues is randomizing patients to the placebo group, especially if other proven effective interventions are available (standard of care). On the contrary, others believe that using placebos in clinical trials to be considered ethical if it has clearly been justified ethically and methodologically.[5] More discussions about the ethical and methodological issues about using placebos in clinical trials is presented in chapter 2.

Randomized controlled clinical trials are the gold standard for assessing medical interventions as they provide the best evidence on both efficacy and safety. The success of these trials depends mainly on keeping the number of individuals recruited into a study to a maximum and the number of dropouts to a minimum. Historically, the participation rate in clinical trials is low. According to the National Cancer Institute (NCI), more than 8000 clinical trials are accepting participants, however, it has been estimated that only 2%–4% of newly diagnosed adult cancer patients participate in clinical trials.[9] The low recruitment rate of potentially eligible patients into clinical trials may delay introduction of efficacious treatments into practice.

Previous studies reported many reasons for patients choosing not to participate in clinical trials. Reasons vary from concerns over side effects, costs, health insurance, transportation or distance to trial site or even the negative public perceptions about research with humans resulting from the Nazi experiments and Tuskegee studies.[10] Other barriers to enrollment include the public's lack of understanding about the scientific methods and purposes of clinical research as well as the ethical safeguards that have been incorporated into the research process to protect participants.[10]

For placebo-controlled clinical trials, it is more difficult to recruit patients compared to clinical trials without a placebo arm. Welton and colleagues investigated whether including a placebo arm in a clinical trial of hormone replacement therapy influenced women's willingness to participate. They found that 39% of women indicated their willingness to enter the trial without a placebo arm compared with 30% of women told about a trial with a placebo arm ($p = 0.06$).[11]

Moreover, in a meta-analysis study by Mills et al. [12], barriers to participate in cancer clinical trials were reviewed, and it was concluded that the presence of placebo or a no treatment group was one of the most common reasons for patients to refuse participation in cancer clinical trials. Another study conducted a survey in the year of 2000 revealed that 31% of the respondents who chose not to participate in a clinical trial reported a fear of receiving a placebo as a major factor in their decision.[13] Existing research suggests that lay people have a somewhat limited understanding of placebos and their effects. A previous study showed that less than half of the patients (47%) were able to provide a correct definition for placebos.[14] Patients' limited or lack of knowledge about placebos can possibly influence their willingness to participate in medical research.

A legal and ethical requirement for conducting clinical trials is that individuals give their voluntary informed consent to participate. The informed consent explains the research aspects of a study related to its rationale, design, standard therapeutic procedures for the given disease, randomization procedure as well as the chance of being randomized to one of the study groups. It is expected that all of this information be communicated and discussed clearly with potential participants.

Subsequent to a participant signing a consent form, an individual's lack of

understanding about the research aspects of a study raises questions about the quality of consent and consenting procedures. Patient education in the basic concepts of clinical trials is necessary to promote an understanding of the informed consent process and enhance a patient's decision-making related to participation in clinical trials. Thus, developing approaches to enhance participant understanding of clinical trial processes as well as of the informed consent process is needed.

In order to improve patients' comprehension of informed consent, many researchers examined the impact of different interventions such as the use of multimedia, enhanced consent form, educational booklets and extended discussion. Recent reviews of interventions aimed at improving patients' understanding of informed consent found few studies that demonstrated significant improvement of patients' understanding for research informed consent.[15,16] The reviewers concluded that no single intervention strategy was consistently associated with improved comprehension and recommended further research in this area.

Discrepancies in these results might be due to a diversity in methods used to measure patient understanding in different patient populations. Palmer and colleagues[16] addressed in their review on the effectiveness of multimedia aids to enhance comprehension of research consent information, the need for a second generation of studies that apply a conceptual framework to identify which types of multimedia tools are useful in which specific contexts, and for which specific population. They suggested the application into future studies a conceptual framework surrounding cognition such as Cognitive Load Theory (CLT).

According to the CLT, new information is processed in the working memory, which has a limited capacity, it can hold up to 5–9 new pieces of information for about 20 seconds.[17] Therefore, with all the information presented in any informed consent, and with the limited memory capacity of patients, cognitive overload may occur which could play a role in reducing patients' comprehension to the elements of clinical trials during the consenting process.[17] CLT aims to develop instructional design principles and strategies to reduce working memory load.

When presenting information to patients, the application of some CLT principles such as the modality principle or the contiguity principle into educational interventions might be helpful to reduce cognitive overload and, therefore, increase understanding. More details about using principles of CLT are presented in chapter 2.

Furthermore, the presence of a theoretical framework is essential to have a better understanding of patients' decision making process related to participation in clinical trials. The Health Belief Model (HBM) will be used in the current study to provide more understanding for patients' willingness to participate in placebo controlled clinical trials. The HBM is composed of six different domains: perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action and self-efficacy.[18] In clinical trials, the decision whether or not to participate may be explained by the extent to which a patient perceives a threat to his or her health and the degree to which a patient believes that trial participation will be effective in reducing that threat, given the perceived effectiveness of a standard treatment or no treatment.[19] The HBM suggests that the component of cue to action is necessary to trigger the decision making process. For that reason, developing educational interventions about placebo controlled clinical trials to work as a cue to action for patients

could potentially decreases patient's perceived barriers about placebo controlled clinical trials. This could increase the likelihood of patients' participation in such trials.

Problem Statement and Study Objectives:

The participation rate of patients in clinical trials is low. Limited knowledge about clinical trials can influence a patient's willingness to participate in medical research. For placebo-controlled clinical trials, it is more difficult to recruit patients compared to clinical trials without a placebo arm. Previous studies have shown that patient education directed at specific aspects of clinical trials improves the informed consent process.[10] Thus, educating individuals about clinical trials and placebos can potentially improve their perceptions about clinical trials and might increase their willingness to participate in them. There are few studies of interventional strategies that have shown significant improvement to a patient's understanding of the informed consent process however, to the best of our knowledge there are no studies of interventions found in the literature review aimed at improving a patient's understanding of randomized placebo-controlled clinical trials.[15]

The study objectives are

Primary Objectives:

1) To design educational interventions (a booklet and a video) based on the principles of Cognitive Load Theory (CLT) to improve a patient's knowledge of placebo-controlled clinical trials.

2) To compare the impact of the educational interventions (booklet, video or both) on a patient's knowledge of placebo-controlled clinical trials.

Secondary Objectives:

1) To compare the impact of the educational interventions (booklet, video or both) on a patient's perceptions (perceived benefits and perceived barriers) related to and their willingness to participate in placebo-controlled clinical trials.

2) To compare a patient's willingness to participate in placebo-controlled clinical trials using 3 different patient allocation ratios of 1:1, 2:1 and 3:1 for a hypothetical study drug to a placebo arm.

3) To examine type of intervention, a patient's perceived susceptibility, a patient's perceived severity and patient characteristics (such as age, gender, education and type of disease) as possible predictors on a patient's knowledge of placebo-controlled clinical trial using a multiple regression model.

4) To examine type of intervention, a patient's knowledge, a patient's perceived susceptibility, a patient's perceived severity and patient characteristics (such as age, gender, education and type of disease) as possible predictors on a patient's perceptions (perceived benefits and perceived barriers) of placebo-controlled clinical trial using a multiple regression model.

5) To examine type of intervention, a patient's knowledge, a patient's perceived susceptibility, a patient's perceived severity, a patient's perception (perceived benefits and perceived barriers) and patient's characteristics (such as age, gender, education and type of disease) as possible predictors on a patient's willingness to participate in placebo-controlled clinical trial using a logistic regression model.

6) To compare the impact of the educational interventions (booklet, video or both) on a patient's knowledge, patient's perceptions (perceived benefits and perceived barriers)

related to and their willingness to participate in placebo-controlled clinical trials among patient groups of oncology, nephrology and diabetes.

Significance:

This study has the following novel and innovative aspects:

- The first known study to design and examine educational interventions related to the use placebos in clinical trials in the medical fields of diabetes, nephrology and oncology.
- The first study to design and produce educational interventions using the principles of CLT.
- The study compared three different interventions at the same time (booklet, video and both interventions).
- The study included a behavioral model to have better understanding for the outcomes.
- The study results may have more generalizability as it included 3 different groups of patients from the clinics of oncology, nephrology and diabetes.

Research Questions and Hypotheses:

The study examined the following research questions and hypotheses:

Research Question 1:

Does adding a patient educational booklet, video or both (the booklet plus video) regarding placebo controlled clinical trials to a standard consent form improve a patient's knowledge of placebo-controlled clinical trials compared to a standard consent form alone?

Hypothesis 1:

There is no difference in a patient's knowledge related to placebo-controlled clinical trials among the educational booklet intervention, video intervention, both interventions (the booklet plus video) and the standard consent form group.

Research Question 2:

Does a patient education booklet, video or both (the booklet plus video) regarding placebo-controlled clinical trials improve a patient's perceptions toward placebo controlled clinical trials compared to a standard consent form?

Hypothesis 2:

There is no difference on a patient's perceptions related placebo-controlled clinical trials among the educational booklet, the video, both interventions (the booklet plus video) and the standard consent form group.

Research Question 3:

Does a patient education booklet, video or both (the booklet plus video) regarding placebo controlled clinical trials improve a patient's willingness to participate in placebo-controlled clinical trials compared to a standard consent form?

Hypothesis 3:

There is no difference on a patient's willingness to participate in placebo controlled clinical trials among the educational booklet, the video, both interventions (the booklet plus video) and the standard consent form group.

Using the Health Belief Model (HBM), the study also examined the following additional research questions:

Research Question 4:

Is there an association between a patient's knowledge about placebo controlled clinical trials and patient's perceptions (perceived benefits and perceived barriers) towards placebo-controlled clinical trials?

Research Question 5:

Is there an association between a patient's perceptions (perceived benefits and perceived barriers) toward placebo-controlled clinical trials and a patient's willingness to participate in placebo-controlled clinical trials?

Research Question 6:

Is there an association between a patient's knowledge about placebo controlled clinical trials and a patient's willingness to participate in placebo-controlled clinical trials?

Rationale for the Previous Research Questions:

A patient's decision to participate in clinical trials may be influenced by their knowledge about and attitudes toward clinical trials. In placebo controlled clinical trials, negative attitudes such as fears of receiving a placebo treatment may be considered a barrier and may reduce a patient's participation.[13] On the contrary, positive attitudes may increase a patient participation. A previous study showed that a clinical trial participants were, as compared with nonparticipants, more positive towards participation.[20] Researchers have previously reported that some educational interventions such as handbooks can change patient attitudes and beliefs towards clinical trials and therefore increase the likelihood of their participation.[10] Moreover, different patients can have different levels of knowledge

which could lead to different perceptions. For example, a previous study showed that patients from cardiology, ophthalmology and rheumatology clinics responded differently to some questions about placebos. Such differences among different patients may influence willingness to participate in placebo clinical trials differently.[21]

Research Question 7:

What are significant predictors (such as age or patient's knowledge score) for a patient's willingness to participate in placebo-controlled clinical trials?

Rationale for Research Question 7:

Using patient knowledge and perceptions to predict patient willingness to participate in placebo-controlled clinical trials is important for planning and conducting future research. It is also important to examine some patient characteristics such as gender, education and social status because they can influence the willingness to participate in clinical trials. A previous study showed that male patients and patients who are older, less well educated, or from lower socioeconomic backgrounds seem more willing to participate in clinical trials.[22]

CHAPTER 2

LITERATURE REVIEW

Introduction:

This chapter consists of a review of the literature related to this study. The literature is reviewed in the following areas:

1. Placebo use in clinical trials: Definitions, ethics and regulations.
2. Patients' reasons and motives for participation in clinical trials.
3. Patients' reasons for non-participation in clinical trials.
4. Perceptions of patients related to the use of placebos in clinical trials.
5. Patient understanding of informed consent and knowledge about clinical trials.
6. Interventions to improve patient understanding of informed consent- systematic review.

The chapter also presents a literature review for the two conceptual frameworks that were used in this study; the Health Belief Model (HBM) and the Cognitive Load Theory (CLT).

Placebo Use in Clinical Trials: Definitions, Ethics and Regulations

Definitions:

The word placebo means, "I shall please".[23] It is generally understood to mean an inert, deceptive treatment given as if it was a real treatment.[24] Shapiro defined placebo as "any therapeutic procedure (or that component of any therapeutic procedure) which is given deliberately to have an effect, or unknowingly has an effect on a patient, symptom, syndrome, or disease, but which is objectively without specific activity for the condition being treated".[4] The Food and Drug Administration (FDA) defines placebo as "an inactive substance that may resemble an active agent but has no medical value."[25]

Placebos can take the form of a medication, diagnostic or therapeutic sham procedure. It is necessary to distinguish between pure and impure placebo: pure placebo

refers to the use of an inert substance or method, while an impure placebo has a pharmacologic effect for a different indication or in a larger dose but is not used for its pharmacologic properties (such as antibiotics for viral illnesses).[24]

Ethics:

Placebos are used in randomized controlled clinical trials to demonstrate the efficacy and the safety of new interventions. Some researchers, however, consider using placebos in clinical trials to be a source of ethical controversy. [6-8] Ethical issues arise from giving patients a placebo as a control treatment especially if other proven effective interventions are available. This might mean that these participants will receive a treatment that does not benefit them, leading to a conflict with the obligation of physicians to do what is best for their patients. Opponents to placebo-controlled trials raise questions concerning the ethical principle of beneficence. In contrast, other supporters say that active controlled trials, the primary alternatives, are not easily interpreted because both the active control and the experimental treatment may display signs of the placebo effects, making elimination of placebo meaningless.

The 2000 revision of the Declaration of Helsinki stated: ‘‘The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods’’ (WHO Declaration of Helsinki 2000: paragraph 29). Taken literally, the Helsinki 2000 wording suggests that placebo controlled trials are appropriate only when no known effective treatment exists for a particular condition, or when the treatment methods that exist are inadequate for a particular subset of patients.[24] This means that Declaration of Helsinki prohibits placebo-controlled trials when there is an available proven intervention.

In order to clarify this issue, the 2008 revision of the Declaration of Helsinki stated in its revised paragraph on placebo: ‘‘The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

– The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
– for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.’’

Similar to what is stated in the declaration of Helsinki, the guidance published by the International Conference of Harmonization (ICH) also clarified the ethical and unethical use of placebos in research as it stated: “ *In the case where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use placebo control*” and “ *In other situations, where there is no serious harm, it is generally considered ethical to ask patients to participate in placebo controlled trial, even if they may experience discomfort as a result, provide the setting is non coercive and patients are fully informed about available therapies*.”

Moreover, some researchers suggested some conditions to ensure patient safety and knowledge during placebo controlled trials. For example, Hoffman proposed the following conditions:[25]

1. each patient is carefully and frequently monitored;

2. early escape mechanisms exist for patients who suffer adverse consequences related to the lack of active therapy;

3. the clinical trial duration is as short as possible; and

4. each participant is clearly informed of and consents to the possibility that he or she will receive placebo rather than standard or experimental treatment.

In summary, the use of placebos in clinical research is considered an ethical practice when there is no current proven intervention, when patients who receive placebos are fully consented and will not be subjected to any risk of serious or irreversible harm, and when all the needed care for patients participating in the research are provided.

Regulations:

Demonstration of safety and effectiveness of a drug is a legal requirement for marketing drugs in many countries. In the USA and in 1938, the Federal Food, Drug, and Cosmetic Act authorized the FDA to obtain reports to assure that drugs marketed to the public are safe and effective. This requires the submission of results from adequate and well-controlled trials capable of distinguishing the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. According to FDA regulation, this usually implies standard clinical trial features such as placebo control groups, randomized assignment to treatment, and blinded outcome assessment.[25]

It has been argued that it is often impossible to show improvement to be unrelated to pharmacological effects of the administered agents without the inclusion of a placebo arm. This is related to the property of assay sensitivity, which is defined as the ability of a trial to

distinguish an effective treatment from a less effective or ineffective intervention.[26] Without assay sensitivity, a trial is not internally valid and is not capable of comparing the efficacy of two interventions.

There are also other advantages of using placebo controls in clinical trials besides proving efficacy including, safety, lack of drug interactions and reducing cost as a result of reducing the required sample size compared to active control clinical trials.[26]

Patients' Reasons and Motives for Participation in Clinical Trials:

Clinical trials rely on the willingness of patients or volunteers to participate. Understanding why patients choose to enroll themselves in clinical trials is crucial to patient recruitment and retention, fulfillment of participant expectations, and to achieve a high quality of informed consent understanding. The current literature shows reasons or motives of patients for participation and includes studies that used quantitative and qualitative methods. Those studies included several different types of respondents such as patients eligible to participate, patients actually considering participation, and patients having already participated in trials.

Motivations of patients for participation in trials can be classified into three broad categories: altruistic, self-interested, and others.[27] Altruistic motives include helping other patients with the same disease and advancing medical and scientific knowledge. Self-interested motives include direct medical benefits such as access to specific medical treatments or tests, extra care and attention, or receipt of associated personal benefits such as financial incentives. Other factors may include pressure or encouragement from family and friends, trust in clinicians, or a sense of obligation to the study doctor or the hospital.

Table 2 summarizes reasons and motivations for adult patients to participate in phase III clinical trials reported in previous studies.

Table 2. Patients' reasons and barriers for participation in clinical trials

A- Studies Reported Both Reasons and Barriers for Participation in Clinical Trials				
Author/Year	Study Design	N	Reasons for Participation	Barriers for Participation
Bevan, 1993[28]	Semi-structured interviews	196	- Altruism - Medical benefit - Asked by the doctor - Out of gratitude to hospital - Persuaded by friends/family - To pass time - Curiosity	- Did not want to alter their current therapy, - Insufficient time - Patient relatives objected participation. - Being too ill - Not wanting to change treatment - Fear of side-effects
Halpern, 2003[29]	Open- ended questions	126	- Personal health benefits - Helping other patients - Contributing to scientific knowledge	- Stop taking current medications - Inconvenience/annoyance - Fear of known side effects
Cunny, 1994[30]	Survey	263	- Altruism - Interaction with volunteers - Interaction with researchers - Money - Improve health - Curious	- Schedule conflicts - Risk involved - Potential discomfort from the medical procedures or medication

Table 2. Patients' reasons and barriers for participation in clinical trials (Continued)

A- Studies Reported Both Reasons and Barriers for Participation in Clinical Trials				
Author/Year	Study Design	N	Reasons for Participation	Barriers for Participation
Locock, 2011[31]	Semi-structured interviews	42	- Personal benefit - Benefiting others	- Desire for a potentially effective drug - Concerns that side-effects - Disproportionate to perceived risk of condition - Preferred standard treatment - Intervention too stressful (self-administered injections) - Personal inconvenience, e.g., extra appointments - Trial information off-putting and too complex information inadequate to make a decision - Unwilling to accept randomization
Jenkins, 2000[32]	Cancer	147	- Altruism - Trust in the doctor - Best treatment available	- I trusted the doctor treating me - The idea of randomization worried me - I wanted the doctor to choose my treatment rather than be randomized by computer

Table 2. Patients' reasons and barriers for participation in clinical trials (Continued)

B- Studies reported only Reasons for Participation in Clinical Trials			
Author/Year	Study Design	N	Reasons for Participation
Cassileth, 1982[33]	Questionnaire	295	- Altruism - Payback med system - Influence of medical profession - Potential benefit to others
Mattson, 1985[34]	Questionnaire	380	- Altruism - Influence of medical profession - Free medical services - Curious - Harmless - Improve health - Payback med system - Reassurance - Have time
Schron , 1997[35]	Questionnaire	4281	- Altruism - Interaction with researchers - Free medical services - Interaction with volunteers - Money - Have time
Yuval, 2000[36]	Questionnaire	150	- To help research - Hoped for better follow-up - Hoped for better treatment - Was frightened to refuse
Wilcox, 1994[37]	Questionnaire	40	- Physician influence - Free care - Choice of medication over surgery - Altruism - To be closely watched - Friend
Penman, 1984[38]	Interview	144	- Trust in physician - Medical benefit - Other physicians agree - Willing to accept the offer - Consent form information - To be a part of research - Physician's information - No better treatment - Trust in hospital - Family wanted it - Benefits outweigh risks

Table 2. Patients' reasons and barriers for participation in clinical trials (Continued)

B- Studies reported only Reasons for Participation in Clinical Trials			
Author/Year	Study Design	N	Reasons for Participation
Jenkins, 2013[39]	Questionnaire	358	- Altruism - Offered best treatment - Trust in the doctor - Wishing the doctor to choose
Madsen, 2002[20]	Questionnaire	167	- Access to the new drug or new diagnostic tool - More closely monitored - Help future patients
Campbell, 2007[40]	Questionnaire	135	- Altruism - Medical benefit - Know other volunteers and medical people who treat me. - Doctor recommendation -Curiosity - Money

Table 2. Patients' reasons and barriers for participation in clinical trials (Continued)

C- Studies reported only Barriers for Participation in Clinical Trials			
Author/Year	Study Design	N	Barriers
Tournoux, 2005[41]	Review	NA	- Preference for a particular treatment option -Fear of random allocation - Desire not to take an experimental treatment. - Concern about information and/or consent - Relationship with medical team
Ellis, 2000[22]	Review	NA	- Fear of random allocation - Preference for either the doctor or themselves to make the decision about which treatment they will receive - Objection to being an experimental subject - Distrust of the medical profession - Lack of knowledge
Grand, 2012[42]	Review	NA	- Concern over loss of control of decision-making - Concerns about toxicity - Geographical isolation from treatment services - Educational status - Knowledge or information about clinical trials - Extra financial burden - Preference for a particular treatment
Go, 2005[43]	Interview	156	- Desire other treatment - Want supportive or hospice care - Not interested - Fear of randomization - Financial - Distance from clinic - Refused further staging

Table 2. Patients' reasons and barriers for participation in clinical trials (Continued)

C- Studies reported only Barriers for Participation in Clinical Trials			
Author/Year	Study Design	N	Barriers
Biswas, 2007[44]	Questionnaire	44	- Inconvenience - Didn't want to be experimented on - Added risk - Study-related reason - Bad timing - Lack of information - Did not want to change treatment to study drug - Randomization - Lack of trust
Lara, 2001[45]	Questionnaire	37	- Desire for other treatment - Distance from the cancer center - Insurance denial
McCarthy-Keith, 2010[46]	Review	NA	- Adverse effects - Participant non-compliance - Failure to follow-up
Brintnall-Karabelas,2011[47]	Phone	965	- Protocol issues - Inconvenience - Financial reasons - Decided to participate elsewhere

Demographics can also affect the willingness of patients to participate in randomized controlled clinical trials. For example, males, patients who are older, less well educated, or from lower socioeconomic backgrounds appear more willing to participate in clinical trials.[22] Additionally, the relationship between patients and their physicians influence the decision to participate in clinical trials as patients who trust their doctor appear more likely to participate in clinical trials when asked.[22]

Furthermore, patient reasons for participation in clinical trials can differ according to the phase of the trial. Troung and colleagues[27] surveyed adult cancer trial participants and parents of pediatric participants across a wide range of trials to assess their reasons for participation. Respondents in phase III trials more often reported altruistic motivations, whereas participants in phase I trials less frequently reported altruistic motivations (p= 0.01). Figure 4 shows the reasons given by participants as very important by the trial phase. Lastly, there are other factors that could influence patients' decision on participation in clinical trials such as trial design or logistics. Table 3 lists different types of influencing factors on patients' participation in clinical trials with examples.[22]

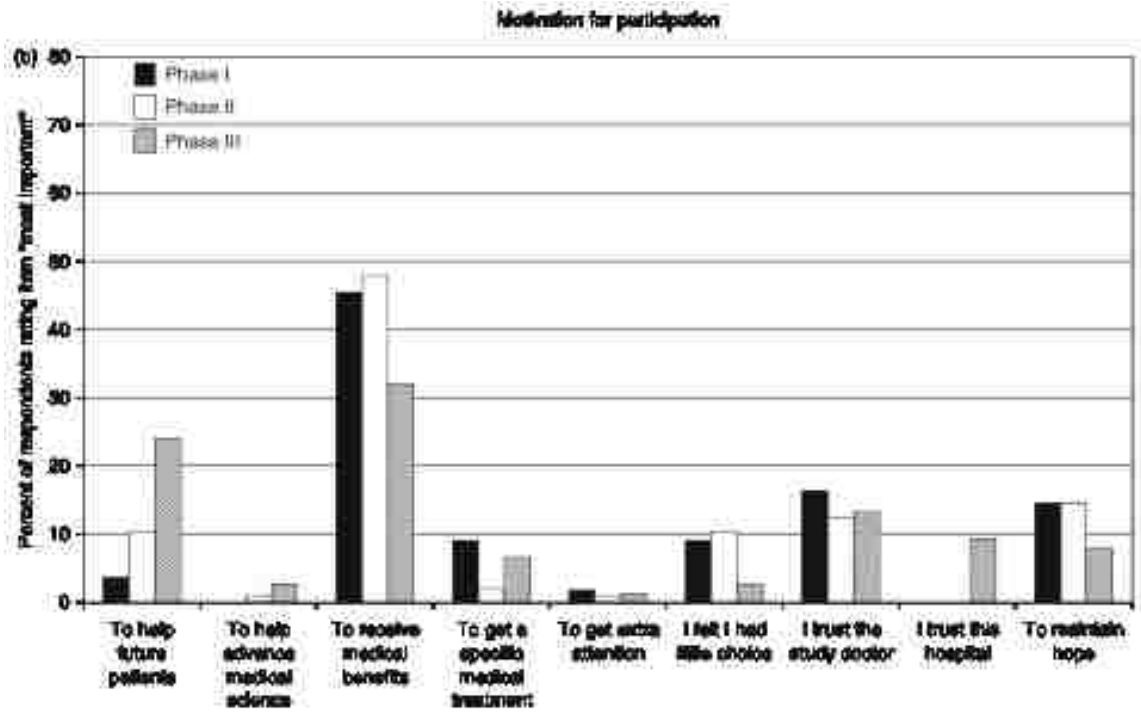


Figure 4: Most important reasons for patient participation in clinical trials by trial phase [27]

Table 3. Factors associated with patient participation in clinical trials [22]

Factor Type	Factor
Doctor	<u>Logistic difficulties</u> - Unaware of trials open for accrual - Lack of time - Lack of resources e.g. data management - Financial constraints - Type of practice (public versus private) - Difficulty with ethics requirements - Identification of eligible patients <u>Personal difficulties</u> - Effect on doctor-patient relationship - Discomfort with randomization - Difficulty with informed consent procedures - Preference for a particular treatment - Overall too difficult (too much time and effort) - Lack of acknowledgment - Opinion of referring doctor
Patient	- Demographics such as age, education - Faith/trust in the doctor - Preference for a particular treatment - Concerns about treatment toxicity - Dislike of randomization, experimentation - Loss of control - Practical issues such as inconvenience - Access to free medical care
Trial	- Poorly designed or complex trial protocols - Presence of a no treatment arm - Large difference between treatment arms, e.g., surgery versus radiotherapy - Toxic therapy being tested - Standard therapy arm not considered standard therapy - Eligibility requirements too narrow - Irrelevant or unimportant trial question

Patients' Reasons for Non-participation in Clinical Trials:

Despite favorable attitudes towards research in general, many people decide not to participate in a clinical trial. Patient participation in clinical research is one of the main challenges faced by researchers today. A previous survey examined a cohort of 41 randomized controlled trials in the United States found that 34% of the trials recruited less than 75% of their planned sample.[95]

Failure to recruit patients may jeopardize the quality of a study by compromising the study power, extend study period and sometimes causing the broadening of the inclusion criteria potentially reducing the validity of the study.[96]

It is important to understand the reasons behind low patient accrual rates in order to increase participation in clinical trials. Understanding some of the reasons for rejecting participation is useful to design future clinical trials. Patient reasons for non-participation vary from fear of randomization, inconvenience, and fear of study drug side effects. Table 2 summarizes patient reasons for non-participation in clinical trials.

Perceptions of Patients Related to the Use of Placebos in Clinical Trials:

For clinical researchers, using placebos is essential to control bias in clinical trials and to isolate the specific effect of a new drug or treatment. But what about those patients who volunteer to take part in clinical research: what do placebos mean to them? Attitudes of potential trial participants toward placebos may influence their

willingness to take part in RCTs. The inclusion of a placebo into a study design can influence patient perceptions about clinical trials, patient willingness to participate in clinical trials, which negatively influence patient recruitment.

The inclusion of placebo controls into a study design can influence patient recruitment. McCarthy-Keith and colleague[46] reviewed 13 randomized trials for treatment of symptomatic leiomyoma published from 2000 through 2008 to evaluate subject enrollment and completion rates. They found that of the five trials that reported an enrollment rate of >70%, only one included a placebo arm. In comparison, out of the four trials that reported an enrollment rate of <51%, 3 had a placebo arm in their design. The authors concluded that the possibility of receiving placebo medication instead of active study drug may have negatively impacted accrual in the placebo-controlled trials.

Another study conducted between 1997 and 2002 in Ontario, Canada, identified characteristics associated with a low recruitment rate in breast cancer clinical trials. [48] The multivariate analysis of that study showed that the use of placebo versus no placebo significantly reduced patients' recruitment in breast cancer clinical trials (RR = 0.80; p = .05).

Agoritsas and colleagues[49] surveyed patients discharged during 1 month from a Swiss public teaching hospital after describing a hypothetical randomized placebo-controlled trial of a new treatment for a respiratory disease. The study team examined three main factors that can influence patient willingness to participate in the hypothetical trial, they were; No side effects (vs. possible side effects), comparison with placebo (vs. current treatment) and public funding (vs. drug company). The

study reported the odds ratios for the willingness to participate for each factor 1.68 (95% C.I: 1.37-2.05) for No side effects, 0.79 (95% C.I: 0.64-0.96) for the placebo arm and 1.03 (95% C.I: 0.85-1.26) for the public funding factor. The study authors concluded that the use of placebo controls was associated with a lower likelihood of participation.

In another study by Welton et al.,[11] postmenopausal women were given information about one of two trials of hormone replacement therapy: one with two active treatments only and one with two active treatments and a placebo. The main outcome measure was willingness to participate in the trial described. The study surveyed 436 postmenopausal women aged 45-64 years from 10 sites throughout the United Kingdom. Of 218 women informed about the trial without a placebo arm, 85 (39%) indicated their willingness to enter compared with 65 (30%) of the 218 women informed about the trial with the placebo arm (p = 0.06). Part of this difference was due to explicit reluctance to take a placebo. Overall, 20 fewer women were prepared to participate in the placebo trial than the no placebo trial, of whom 11 (55%) indicated not wanting to take a placebo as a reason for their decision. This shows that the inclusion of a placebo did directly influence some women's decisions.

More interestingly, when the placebo allocation rate increases in a clinical trial, patient willingness to participate decreases. Halpern and his team described a hypothetical placebo controlled trial of a new antihypertensive drug to patients who would be eligible for ongoing phase III trials.[29] They assessed willingness to participate in 62 patients after revealing, in random order, that 10%, 30%, and 50% of patients would receive placebo. Using a logistic regression model, patient

willingness to participate declined as the placebo randomization rate increased. The proportions of patients willing to enroll if 10%, 30%, and 50% of patients would receive placebo were 41%, 38%, and 37%, respectively. When patients in the study were directly questioned, 34% said the percentage of patients receiving placebo strongly influenced their participation decisions.

Moreover, many patients see the inclusion of placebos in clinical trials as barrier for participation. For example, Carrol and colleagues[50] conducted semi structured interviews for 26 patients with Pulmonary Arterial Hypertension (PAH) to understand the motivations and barriers for participating in RCTs. The interviews revealed that 10 (38%) of the patients expressed their concerns about placebos. In that study**,** one patient stated, "*You were going pretty good until you said I would have to stop taking my (endothelin receptor antagonist) and take the experimental drug, not knowing whether or not I had the placebo or the real thing. That is a matter of concern to me*".[6]

Comis and colleagues[13] surveyed 1000 adults and 5980 cancer patients to understand their attitudes toward participation in cancer clinical trials. Only 14% of cancer patients were aware of clinical trials, of whom 71% had never participated in any trial. Of the non-participants, 31% cited that fear of receiving placebo was their reason for choosing not to participate. Moreover, more than 50% of public and more than 55% of unaware patients about clinical trials expressed the likelihood of getting placebos as one of their negative attitudes towards clinical trials. Figures 5 and 6 depict those results from the survey conducted by Comis et al.

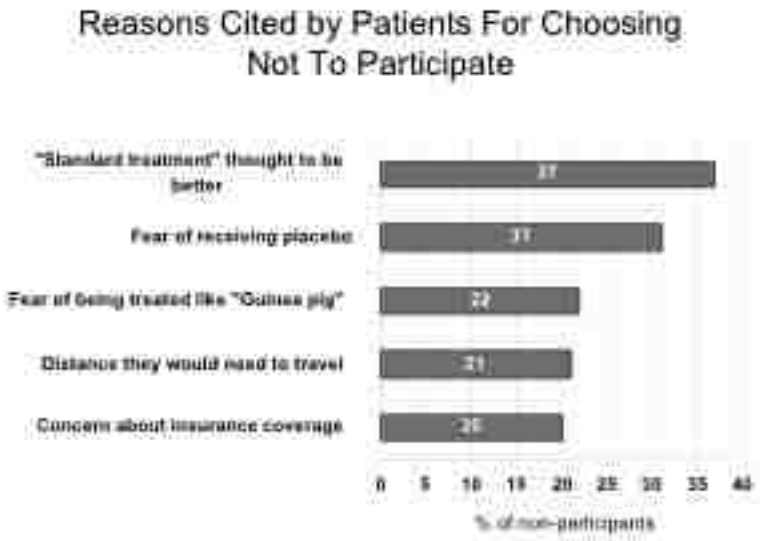


Figure 5: Reasons listed by Non-participant patients [13]

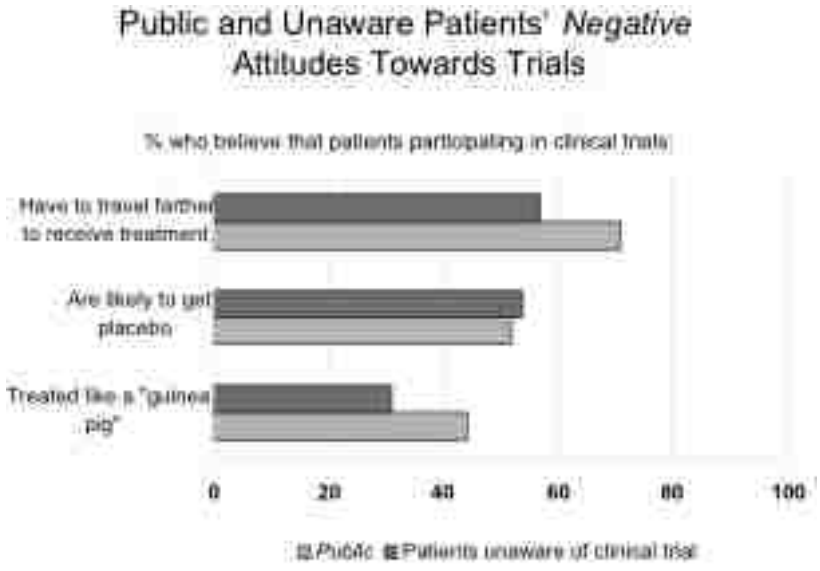


Figure 6: Reasons listed by public and unaware patients of clinical trials [13]

Patient Understanding of Informed Consent and Knowledge about Clinical Trials:

In clinical research, the idea of written informed consent dates back to 1900, when Walter Reed obtained written consent from patients in his research on yellow fever in Cuba.[51] The Nuremberg Code was developed in 1947, which established a set of principles and guidelines for the ethical conduct of clinical research. Informed consent was established as a result of these principles.

In 1964, the World Medical Association Declaration of Helsinki established worldwide ethical principles for medical research that involved human participants and provided more protection for research participants. It states that:

"In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study".

Many years later and in 1979, the Belmont Report formulated ethical basis for clinical research in a form of three main principles which are; "autonomy", "beneficence", and "justice".[51] The key aspect of autonomy is voluntary consent based on full understanding of potential risks and benefits.

Approximately 2.3 million patients participate in more than 80000 government and industry sponsored trials each year in the United States.[52] The process of informed consent includes the following five elements: voluntarism, capacity, disclosure, understanding, and decision.[53] For research participants, signing

of the consent form is meant to indicate their agreement to participate in the trial and confirm that they understand the aim and risks of the trial and their participation in it. Signing such a document, however, does not always represent understanding. Patients might have incomplete or incorrect understanding of matters relevant to an informed decision to join a clinical trial.

There are several studies that have assessed patient understanding and comprehension of several aspects of the informed consent. Falagas and his colleagues[53] conducted a systematic review to identify all relevant studies between 1961–2006 which assessed patient understanding of different aspects in the process of the informed consent. The study included 30 articles in the review of which 11 studies were conducted in patients with cancer. The review covered aspects in the informed consent such as the aim of the study, the process of randomization, voluntarism, withdrawal, and the risks and the benefits of treatment. The review found that patients achieved adequate understanding for the aim of the study (14 of 26 studies, 54%), the process of randomization (4 of 8 studies, 50%), voluntarism (7 of 15 studies,47%) and withdrawal (7 of 16 studies,44%). They study also found that patients achieved adequate understanding for the risks and for the benefits of treatment in 8 of 16 (50%), and 4 of 7 (57%) of the studies included in that review. The study authors concluded that further attention should be drawn on enhancing patient understanding regarding several components of the informed consent process for clinical research. Unfortunately, this systematic review did not examine or report patient understanding for the placebos in the informed consent.

To the best of our knowledge, there is only one study that examined patient understandings of placebos and their role in clinical trials. Pope and colleagues [21] surveyed patients from 14 clinical trials conducted in the departments of rheumatology, ophthalmology, and cardiology to assess the level of understanding of some concepts used in the trials such as the use of placebos, the chance of allocation to placebo and the reason for using placebos. The study showed that only 13% of the study participants demonstrated full understanding of the role of placebo in clinical trials, 56% indicated a partial understanding, and 30% reported that they did not know. Subjects with post-secondary education were more likely to partially or fully understand (66%) why placebo was used in the clinical trial than high school (54%) and elementary school (22%) educated subjects ($p < 0.0003$).

A possible explanation for a patient's inadequate understanding of the information in the informed consent process, is not reading or only skimming the consent forms.[54] Common reasons for not reading these types of documents included trusting the researcher or person preparing the document, not having time to read the document, and having had the document orally explained. More importantly, even when research participants do carefully read consent forms, their comprehension of and recall for the information is affected by readability and vocabulary of the document. It can be also affected by their age, education, and cognitive and mental status. Not reading or not understanding informed consent documents could have major consequences on patients to the extent that some participants in some medical research studies did not even realize they were participating in research.[54]

Interventions to Improve Patient Understanding of Informed Consent – Systematic Review:

As it has been discussed earlier, patients might have an incomplete or incorrect understanding of aspects relevant to the informed consent process. As a result, many researchers have examined the impact of different interventions to improve patient comprehension of informed consent.[15,16] These interventions included the use of multimedia, enhanced consent form, educational booklets and extended discussion.

For enhanced consent forms, investigators used 4 basic strategies: Condensing the length of the form, revising the content of the form to make it more comprehensible and readable, improving formatting through the use of techniques like larger font size and italics, and adding graphics. In contrast, the term multimedia specifically refers to integration of two or more forms or channels of information, such as auditory (voice and other sound), visual (still and motion pictures, animation, graphs), and/or text.

Yet it remains unclear whether multimedia tools are effective in enhancing comprehension of consent information. Previous researchers conducted systematic reviews to answer the question of which intervention works better to increase participants' understanding. Flory and Emanuel [15] conducted a systematic review for studies from 1966 to March 2004 that examined interventions to improve research participants' understanding of information presented in the informed consent process. Thirty studies described 42 interventions that met their inclusion criteria. There were 12 trials of multimedia interventions. Only 3 of these trials showed

significant improvement in understanding. Fifteen trials examined enhanced consent form interventions. Only 6 of these studies showed significant gains to understanding. Five trials of extended discussion evaluated interventions with 3 showed significant improvement in understanding (all p =.001) and 2 showed trends toward improvement (p=.054 and p=.08). The remaining 10 trials examined test-feedback and other miscellaneous interventions with no significant results. Overall, 12 studies showed that research participants with higher education or reading levels had significantly higher understanding scores. The authors also concluded that increased age was associated with lower understanding in 5 studies that enrolled participants with mean age of older than 50 years (all p=.05)

In another systematic review conducted by Palmer and his colleagues[16] to assess the effectiveness of using multimedia interventions on a patient's understanding of informed consent. They included 20 studies published between December 1988 and January 2012 in their review. Ten studies (50%) found multimedia interventions were associated with significantly better understanding (either overall comprehension or understanding of key informational components) of disclosed information than was achieved without multimedia aids. Only four studies (20%) reported no significant differences between multimedia and comparison consent procedures. The study authors concluded that multimedia interventions appeared to have at least partial benefits on improving patients' comprehension. This conclusion contrasts with that from the previous review by Flory and Emanuel[15] in which they noted that multimedia tools often failed to improve research participants' understanding. Such discrepancy in results between

the two reviews could be the result of including different studies from different time frames. Therefore, in order to have the most recent studies in this area, we conducted our own systematic review. We used the following searching terms: "clinical trials AND consent AND understanding" OR "clinical trials AND consent and comprehension" using PubMed with the following inclusion criteria:

- Interventional study of comprehension of informed consent to participate in a clinical research study,
- Studies conducted in a nonpsychiatric adult population
- Studies written in English

In order to include only studies with similar patient groups to the groups included in this study, we excluded the following population groups: (Exclusion criteria): Studies conducted for:

- Surgery
- Parents
- Children
- HIV
- Biobank or genetic research
- Blood donation/transfer
- Pregnancy.

Our research included studies until the end of the year 2013. We also identified studies through the cross-references strategy from the two previous systematic reviews [15,16] to include studies that were not previously identified in our searching strategy. We were able to identify 675 hits. After initial screening by title, 97 studies

were included. After an abstracts and text review, 15 additional studies were included in the final screening. Only 1 article was not retrievable. Seven studies were identified through the cross-references strategy. A total of 21 studies were included in the final review. Among the 21 studies, there were 9 studies (42.8%) that reported significant results in improving patents' understanding of informed consent. These 9 studies included; 3 multimedia, 5 enhanced informed consent and 1 telephone discussion intervention. In general, the understanding scores for the significant results ranged from 3.3% to 20.1% of improvement in patients' understanding. For studies with multimedia interventions, the improvement in patients' understanding score ranged from 0% to 17% while for the enhanced informed consent or booklet interventions it ranged from 2% to 20.1%. Table 4 summarizes all the included studies in our review.

Table 4. Results of the systematic review for interventional studies to improve patient comprehension of informed consent

Author/year	Population	Intervention	Control	Measurement method	Comments	Scenario	Size	Control Score %	Intervention Score %	P value
Rowbotham/2013	Clinical research professionals, and patients drawn from a variety of outpatient practice settings.	An interactive presentation using an iPad device	Paper ICF	Quiz consisted of 7 multiple-choice questions	Participants had three chances to answer correctly	Hypothetical	55	58%	75%	0.001
Benatar/2012	Inpatients setting	A short ICF + booklet, or a simplified ICF + booklet.	Standard ICF	Questionnaire	3-24 hours later	Hypothetical	282	52	52 vs. 62 vs. 62	0.05
Hoffner/2013	Cancer	ICF + video	ICF	Questionnaire	Watched at home , measured after 1 week, 20 min video	Real	90	90	90	NS
Knapp/2011	Public	Revised ICF	Paper ICF	Interview	Participants had three chances to answer correctly	Hypothetical	123	Could not understand only 0.3 items	Could not understand 0.2 items	0.17

Table 4. Results of the systematic review for interventional studies to improve patient comprehension of informed consent (Cont'd)

Author/year	Population	Intervention	Control	Measurement method	Comments	Scenario	Size	Control Score %	Intervention Score %	P value
Paris/2010	Patients with stroke, DM, or OSAS	Simplified paper document with systematic readability improvement or Simplified paper document developed by a working group of clinical research nurse, IRB member, and healthy volunteer	Standard ICF	Questionnaire		Hypothetical	115	67	69 69	NS NS
Hutchinson/2007	Cancer	Supplementary 10 min. video. Vignettes, visual aids, voice-over, and graphics. Patients allowed to take video home° + ICF	ICF	Questionnaire	Watched at home , measured next visit, pre –post test	173	90	NA (Median change in knowledge =5)	NA	0.011

Table 4. Results of the systematic review for interventional studies to improve patient comprehension of informed consent (Cont'd)

Author/year	Population	Intervention	Control	Measurement method	Comments	Scenario	Size	Control Score %	Intervention Score %	P value
Paris/2007	Healthy	Simplified paper document with systematic readability improvement	Paper ICF	Questionnaire		Hypothetical	200	78.2	81.7	0.05
		Simplified paper document developed by a working group of clinical research nurse, IRB member, and healthy volunteer							82.6	0.017
		Simplified paper document developed by a working group and by systematic readability improvement							81.5	0.05

Table 4. Results of the systematic review for interventional studies to improve patients' comprehension of informed consent (Cont'd)

Author/year	Population	Intervention	Control	Measurement method	Comments	Scenario	Size	Control Score %	Intervention Score %	P value
Graham/2005	Students	Educational Booklet	No Booklet	Questionnaire		Hypothetical	90	82.6	88.7	0.001
Agre /2003	Cancer	Computer, video, booklet	ICF	Multiple choice questions		Real	204	68,71,69.9	68.2	NS
Coyne/2003	Cancer	Readability improved	paper ICF	Interview	Interview after 1 week	Real	207	69	72	0.2
Bjorn/1999	Hypertensive and women for sterilisation	Revised ICF	ICF	Questionnaire	% of understanding all of it	Real	135 100	27 14	31 21	NS 0.001
Davis/1998	Cancer + Healthy	Revised with patient input, readability improved from college to 7th grade level, shortened, booklet format, graphics	paper ICF	Interview		Hypothetical	108	56	58	NS

Table 4. Results of the systematic review for interventional studies to improve patients' comprehension of informed consent (Cont'd)

Author/year	Population	Intervention	Control	Measurement method	Comments	Scenario	Size	Control Score %	Intervention Score %	P value
Aaronson/ 1996	Cancer	Standard consent plus telephone-based nursing intervention,	A standard ICF	interview	After 1 week	Real	180	66.3	83.1	0.001
Young/ 1990	Healthy	Readability improved ICF	Paper ICF	Not reported		Hypothetical	666	64	67	0.001
Dresden/ 2001	Asthma	Modified, shorten ICF	A standard ICF	questionnaire		Hypothetical	100	72	88	0.001
Taub/ 1980	Elderly	Readability improved	Standard	Not reported		Real	56	NR	NR	NS
Taub/ 1986	Cardiac	Readability improve	Paper ICF	Not reported		Real	188	71	74	NS
Taub/ 1987	Elderly	Readability improved	Standard	Not reported		Real	235	68	70	NS
Norris/ 1990	Duodenal ulcer	ICF + Video	Standard	Questionnaire	Answered more than 8/10 questions	Real	200	30	100	Significant
Campbel/ 2008	Outpatient clinics	Information handbook	Completed the questionnaire without reading the handbook	Questionnaire		Hypothetical	146	64.4	84.5	<0.001
Karunaratne / 2010	Diabetes and Endocrinology	Computer-based presentation	A per-based information	Questionnaire		Hypothetical	60	73	82	0.005

Our review showed that different types of interventions to improve understanding showed varied results. Possible explanations for inconsistency in the results could be due to the fact that the included studies in the review examined the interventions differently. For example, in different patient populations (healthy vs. patients), different diseases, used different methods and time points to measure patients' comprehension. Another possible reason is weather these studies used real or hypothetical scenarios as well as if they measured patients' understanding of specific information in the informed consent or general knowledge about clinical trials.

A very interesting finding is that none of the interventional studies examine a specific theory or model to explain or understand the impact of the intervention on patients' comprehension. Most of the interventions used in the previous studies were developed based on response to suggestions or feedback from clinicians, researchers, bioethicists, participants, or a mixture of representatives from these relevant stakeholder groups. Flory and Emanuel [15] in their review highlighted the importance of including a theory or a model which will provide information not only on what does and does not work, but also gives insight into why an intervention is or is not effective, which then helps guide further refinements or application to the consent process for new studies. They suggested to use theories such as Cognitive Load Theory (CLT) which will provide a framework and a ground for future research in this area.

Cognitive Load Theory

Introduction:

Current theories of learning are based on the interaction among 3 memory systems and the processes that move information among them. The 3 memory systems are the visual and auditory sensory memories, working or short-term memory, and long-term memory.[57]

Working memory is the central processor for learning and thinking, but unfortunately it has limited storing capacity. The new information must be rehearsed in working memory and then transferred to be stored in the long-term memory, which has a large storage capacity. The process of storing information in the long-term memory is called encoding. However, encoding into long-term memory is not sufficient because all the new knowledge and skills encoded into long-term memory must be retrieved into working memory when needed to perform a skill or task. The information retained in and processed by the working memory is referred to as "cognitive load."[58]

Cognitive Load Theory:

Cognitive Load Theory (CLT) was initially developed in the 1980s.[59] The human cognitive system has a limited working memory that can hold no more than five to nine information elements and actively process no more than two to four elements simultaneously. Working memory is able to deal with information for no more than a few seconds and almost all information is lost after about 20 seconds unless it is refreshed by rehearsal.

Types of Cognitive Load

There are 3 types of working memory load or cognitive load:

1- Intrinsic Load: Related to the content such as the difficulty or complexity of the material being presented

2- Extrinsic Load: Related to the manner in which the material is presented (e.g. format, use of white space, font size, or word choice)

3- Germane Load: Refers to the working memory resources used to deal with the presented information to achieve comprehension.

The balance between the three types of cognitive load is essential to achieve a better learning process. CLT aimed to develop instructional design principles and strategies to reduce working memory load. The application of some principles from CLT into educational interventions when presenting information might be helpful to reduce cognitive overload and, therefore, increases understanding .[57-59] The theory emphasizes that these working memory capacity and duration limitations only apply to novel information obtained through sensory memory.

CLT Principles and Strategies:

CLT aimed to develop instructional design principles and strategies based on a model of human cognitive architecture. Some of these principles and strategies are explained below:

1) Modality Principle:

According to the modality principle, the use of video as a communicative device, with dynamic images and audio narration, should be superior to print-based text.[60] The modality principle asks the question, ‘‘Is learning better when

instructional visuals are described with text or with audio narration?'' The use of audio to convey verbal information frees visual working memory to process related images, while print-based text forces readers to split visual working memory resources between written words and pictures.[60]

The use of video would allow for greater allocation of cognitive resources towards comprehension of intrinsic components of the intended message. Previous research concluded that learning is deeper when the limited capacity of working memory is maximized by coordinated inputs into the visual and auditory subsystems, rather than just the visual subsystem, as is the case when text is used to describe visuals.

2) Contiguity Principle:

When designing instruction materials that contain graphics, some of those graphics must be explained by text. In these situations, a number of researchers have shown that integrating the text into the graphic is better than separating the text.[57] From comparisons in five experiments, Mayer [57] found a median gain in learning of 68%, with an effect size of 1.12 for lessons that integrated text into illustrations.[57] Less mental effort is involved in integration of pictures and text when they are placed physically close to each other on the page or screen. Mayer referred to this as the contiguity principle of instruction. Figure 7 and 8 show two images in which one image applies the contiguity principle and the other violates it.

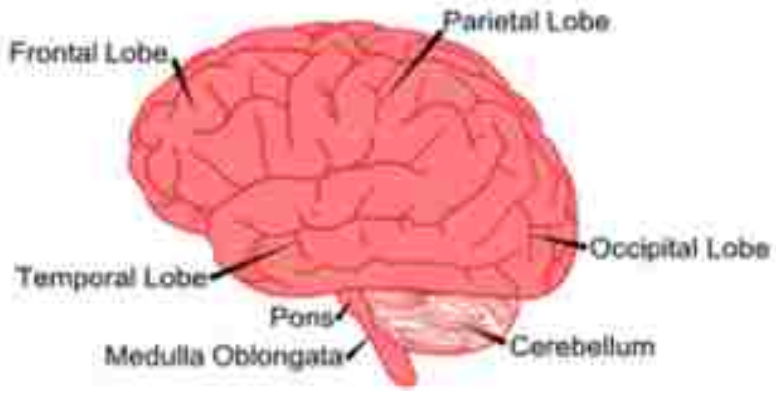


Figure 7: The contiguity principle is followed because the labels for the parts of the brain are placed physically near the parts of the brain to which they correspond.

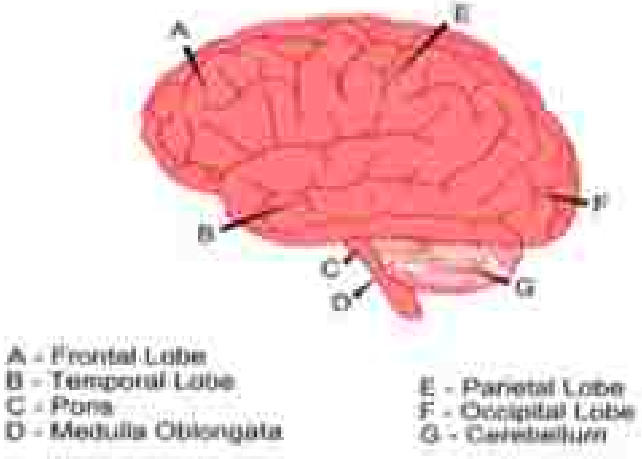


Figure 8: The contiguity principle is violated because the labels indicating the parts of the brain are physically separated from the image of the brain.

3) Redundancy Principle:

Repetition of concepts is used to reinforce previously presented material, but can become redundant, thereby increasing intrinsic cognitive load.[58] An appropriate balance between redundancy and reinforcement is required to strengthen connections between data in the working and long-term memory. Mayer's [57] redundancy principle states that students learn better when they are presented with animation and narration compared to animation, narration, and a visual representation of the text. The redundancy of the text overloads the working memory and reduces attention from key information.

4) Synchronize Audio and Visual Information:

A study by Mayer [58] showed that students learn better when corresponding information is presented simultaneously in space and time. When corresponding words and pictures are separated in time due to lecture constraints or poor design of educational materials, the cognitive load increases by forcing learners to retain a piece of information to understand its context at a later.

Table 5. Depicts CLT principles and strategies and their effect.

CLT Principle/Strategy	**Goal**
Text simplification and minimization	Decrease intrinsic load
Contiguity	Decrease extrinsic load Optimize germane load
Multimodal	Decrease extrinsic load Optimize germane load
White space	Decrease extrinsic load Optimize germane load
Avoidance of background music	Decrease extrinsic load Optimize germane load
Synchronize audio and visual Information	Decrease extrinsic load Optimize germane load

5) Other Best Practices:

Effective educational materials should allow users to focus mental energy on understanding the presented information. They should also minimize the proportion of mental resources needed to process the presented information of the educational material by avoiding the use of complex wording or background music.[60]

The presence of negatively formulated statements can also hinder memory for information, as readers are more likely to misremember negatively worded health information than positively worded ones. For example, older readers are more likely to incorrectly endorse health statements that begin with negative wording compared to positive ones.[60]

Health Belief Model:

The HBM was originally developed in 1950s.[61] The HBM is used to examine patient motivations for adapting a health-related behavior and used in assessing health-behavior interventions.[73] The HBM includes six key domains which influence health behaviors: perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action and self-efficacy.[73] Perceived susceptibility addresses patient's beliefs about their risk for getting a condition; whereas perceived severity relates to the patient's concerns about the seriousness of a condition or illness. Perceived benefits are related to the outcomes of a certain behavior to reduce their susceptibility to or severity of an illness. Perceived barriers identify patient's concerns or negative beliefs about a health behavior. Cues to action are strategies or information sources that promote adoption of a behavior. Self-efficacy measures the patient's confidence to adopt a behavior or take action. The relationships among the HBM concepts are easy to understand and easy to relate to practice. [18-19]

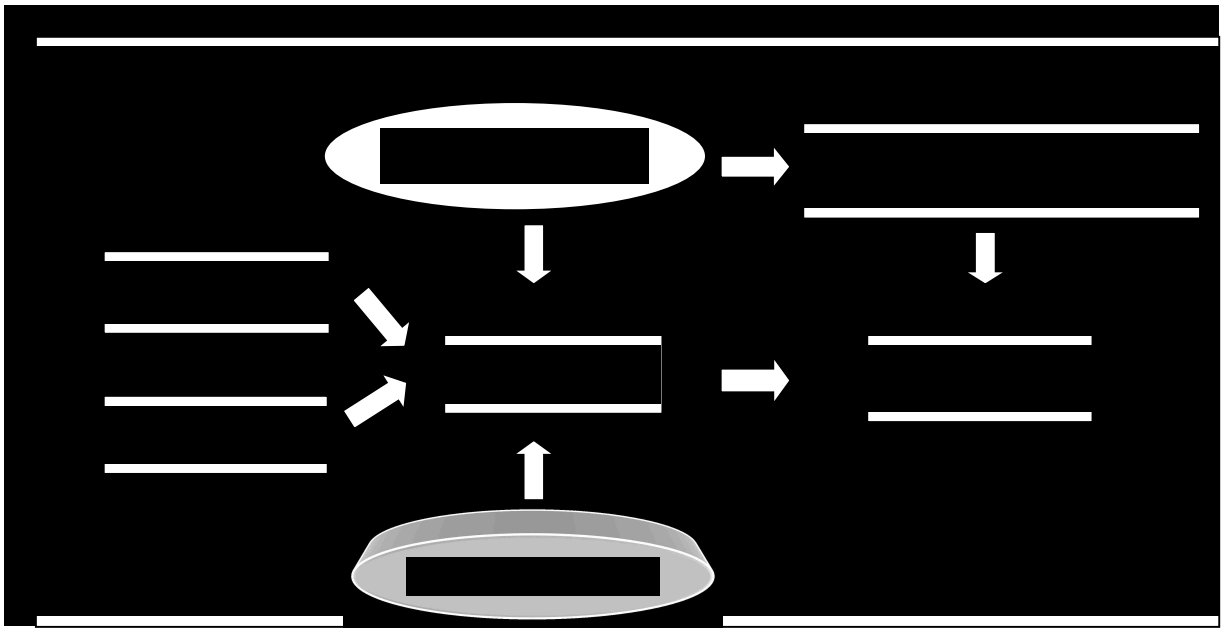


Figure 9. The health belief model components [96]

Table 6. Definitions of the health belief model components [73]

HBM Component	Definition
Perceived Susceptibility	Patient's beliefs about their risk for getting a condition
Perceived Severity	Patient's concerns about the seriousness of a condition or illness.
Perceived Benefits	Patient's belief related to the outcomes of a certain behavior to reduce their susceptibility to or severity of an illness
Perceived Barriers	Identify patient's concerns or negative beliefs about a health behavior
Cues to Action	A stimulus that can trigger appropriate health behavior
Self-Efficacy	Patient's confidence to adopt a behavior or take action

Summary:

Placebos are essential methodology tools in RCT's to control for bias. Existing research suggests that lay people have somewhat limited understanding of placebos

and their effects. Moreover, some patients and the public have negative attitudes toward using placebos in clinical trials. As a result, the inclusion of placebo controls into a study design is considered a barrier for participation and can influence patient recruitment into placebo controlled clinical trials.

Educating patients about some basic concepts of clinical trials and the use of placebos is necessary to promote understanding and enhance patient decision-making related to participation in placebo-controlled clinical trials. Thus, developing approaches to enhance participant understanding of trial processes as well as of the informed consent process is needed.

In order to improve patient comprehension of informed consent, many researchers examine the impact of different interventions such as the use of multimedia, enhanced consent form, educational booklets and extended discussion. However, recent reviews of interventions aimed at improving a patient's understanding of informed consent found few studies that demonstrated a significant improvement in a patient's understanding for research informed consent. The reviewers concluded that no single intervention strategy was consistently associated with improved comprehension and recommended further research in this area.

Palmer and colleagues [16] addressed in their review on the effectiveness of multimedia aids to enhance comprehension of research consent information the need for a second generation of studies that apply a conceptual framework. This will help to identify which types of multimedia tools are useful, which specific contexts and for which specific population. They suggested the application of a conceptual framework surrounding cognition such as Cognitive Load Theory (CLT) into future studies.

CHAPTER 3

METHODS

Introduction:

This chapter summarizes the research methods that were used in this study. It describes the procedures and conceptual frameworks that were utilized in designing and producing the educational interventions. The chapter outlines the characteristics of the targeted population, sampling frame, inclusion/exclusion criteria, sample size calculation and the process of randomization. The chapter provides a detailed description of the survey instrument that was used for the evaluation of the effectiveness of the interventions. lastly, the chapter describes all the statistical tests used to analyze the collected data.

Study Design and Population:

The present study is a randomized, cross sectional study. A paper-based questionnaire was used to collect patient knowledge, perceptions and their willingness to participate in placebo-controlled clinical trials. Study participants were randomly assigned to one of the 4 study groups;

1- Educational booklet plus standard consent form
2- Educational video plus standard consent form
3- Both the educational booklet and the educational video plus standard consent form
4- Standard consent form alone as a control group.

Study participants were selected from patients visiting outpatient clinics at the University of New Mexico Hospital, which receives more than 450,000 outpatient visits every year.[62] The questionnaire was administered to study

participants visiting the outpatient nephrology, diabetes or oncology clinics. Patients had the following inclusion criteria:

1. Patients have to be 18 years or older
2. English speaking
3. Able to read English
4. Have to be established patients with at least one prior clinic visit in the past year to be included in the study
5. Completed the informed consent process.

Participants in the intervention groups: 1) read the educational booklet plus read a standard consent form, 2) watched the video plus read a standard consent form or 3) read the educational booklet plus watched the video plus read a standard consent form. All intervention groups were asked to answer the self-administered questionnaire. For the control group, participants read a standard consent form and then answered the self-administered questionnaire.

Conceptual Framework:

This study applied principles and strategies based on Cognitive Load Theory (CLT) in the development of the educational interventions about placebo-controlled clinical trials. This study also applied the Health Belief Model (HBM) components to explain patient decisions regarding their willingness to participate in placebo-controlled clinical trials.

CLT and Educational Interventions:

CLT assumes that the human cognitive system has a limited working memory. There are 3 types of cognitive load:

1- Intrinsic Load: Related to the content such as the difficulty or complexity of the material being presented

2- Extrinsic Load: Related to the manner in which the material is presented (e.g. format, use of white space, font size, or word choice)

3- Germane Load: Refers to the working memory resources used to deal with the presented information to achieve comprehension

The balance between the three types of cognitive load is essential to achieve a better learning process. CLT is aimed to develop instructional design principles and strategies to reduce working memory load. The application of some principles from CLT into the educational interventions when presenting information about placebo controlled clinical trials to patients might be helpful to reduce cognitive overload and therefore increases their understanding to such information.

First, in order to reduce the intrinsic load, information presented in the educational interventions were simple and easy to be read. Effective, simple and easy to understand educational interventions should avoid technical jargon, use positive wording and avoid negations. They should also exclude distracting or extra information and divide information into manageable pieces.

Second, there are some strategies based on CLT to reduce the extrinsic load. The contiguity principle which is integrating the text into the graphic was used in the development of the educational interventions. For the video intervention, the modality principle was applied to reduce extrinsic load. According to the modality principle, the addition of using audio narration into the use of video to present information with dynamic images will free visual working memory to process related

images, while print-based text forces readers to split visual working memory resources between written words and pictures which will increase the cognitive load.

A third design principle for the video intervention is related to synchronize audio and visual information in which all corresponding words and pictures were presented simultaneously in space and time. This principle is associated with a higher germane load and improves learning outcomes.

Table 7: CLT principles and strategies incorporated in the educational interventions used in the present study.

CLT Principle/Strategy	**Goal**	**Booklet**	**Video**
Text simplification and minimization	Decrease intrinsic load	√	√
Contiguity	Decrease extrinsic load Optimize germane load	√	√
Multimodal	Decrease extrinsic load Optimize germane load	NA	√
White space	Decrease extrinsic load Optimize germane load	√	√
Avoidance of background music	Decrease extrinsic load Optimize germane load	NA	√
Synchronize audio and visual Information	Decrease extrinsic load Optimize germane load	NA	√

Health Belief Model:

The HBM was the theoretical framework that was applied in this study to provide a better understanding of patients' decision making process related to the participation in clinical trials. The HBM is composed of six different domains: perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action and self-efficacy. The HBM hypothesizes that behavior depends mainly upon: (1) the value placed by an individual on a particular goal (value); and (2) the individual's estimate of the likelihood that a given action will achieve that goal (expectancy). [19]

The decision whether or not to participate in clinical trials may be explained by the extent to which a patient perceives a threat to his or her health and the degree to which a patient believes that clinical trial participation will be effective in reducing that threat, given the perceived effectiveness of standard or no treatment.

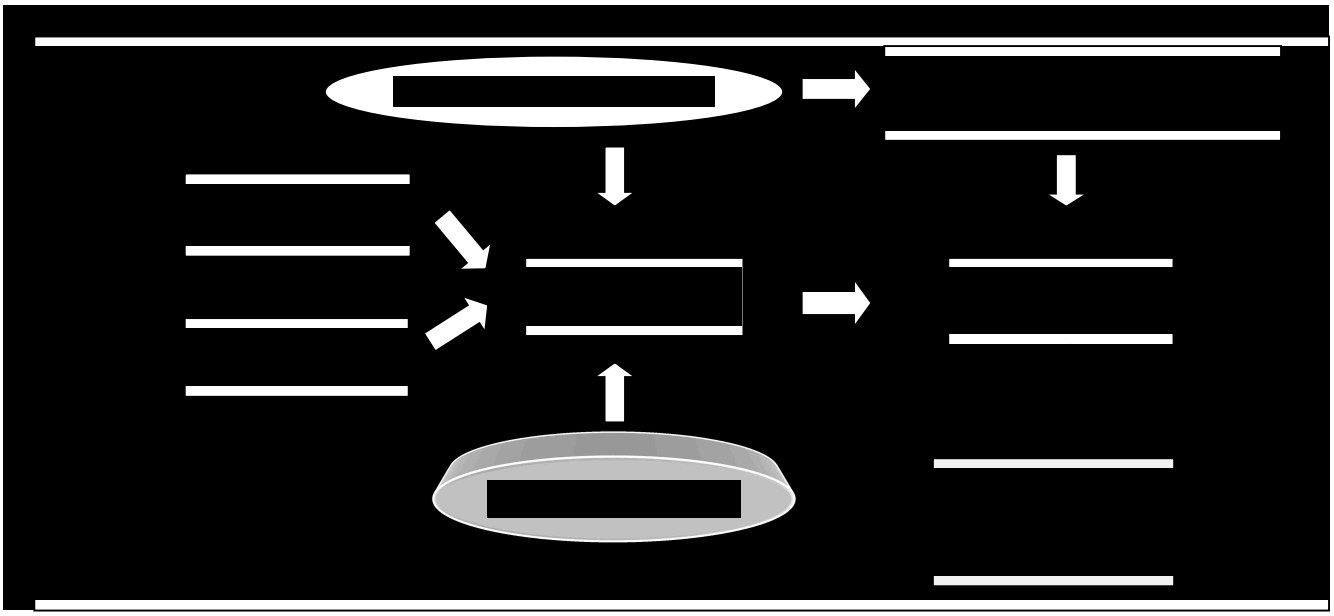
In correspondence to the HBM components, a patient's perceived susceptibility is the risk of contracting a health condition. This also includes acceptance of a diagnosis and susceptibility to illness in general. Patient's perceived severity is the feelings concerning the seriousness of contracting an illness or leaving it untreated. Based on the susceptibility and severity, patients will try to seek medical attention. This might include the option of participation in a placebo-controlled clinical trials. Patients then will weigh the benefits (perceived benefits) from participation and taking the study medication compared to routine medical care. Moreover, patients may also consider all the potential negative aspects of the participation in placebo clinical trials such as negative attitude, distrust or limited

knowledge about placebos. The greater benefits and fewer disadvantages or barriers a patient perceives, the greater the possibility that he or she will participate in placebo-controlled clinical trials.

The HBM suggests that the component of cue to action is necessary to trigger the decision making process. For this reason, the educational materials about placebo controlled clinical trials will work as a cue to action for patients. This may lead to decrease patients' perceived barriers and increase perceived benefits about placebo-controlled clinical trials and therefore increases the likelihood to participate in them.

The last component in the HBM is self-efficacy, which measures the patient's confidence to adopt a behavior or take action, e.g. participation in a clinical trial. Individuals usually do not try to do something new unless they can do it and must feel competent or self-efficacious to overcome perceived barriers in taking action. Therefore, patient's previous participation in clinical trials was used to represent the component of self-efficacy.

The likelihood of a behavior in the HBM is modified by other variables such as age or gender. A number of demographic characteristics have been reported to be associated with the willingness to participate in randomized clinical trials. Previous studies have shown that males, patients who are older, less educated, or from lower socioeconomic backgrounds are more willing to participate in clinical trials.[22] Therefore, the present study collected such important patients' demographics.



The Interventional and Control Materials:

The interventional materials included the educational booklet and the educational video. Below is the description for each of the two interventions.

1- The Educational Booklet:

The booklet was developed based on review of other similar clinical trials information materials as well as from the input from the study team. The booklet was entitled "Learn More About Placebo Clinical Trials" (Appendix A). The two sided, one-page booklet described the following information about placebo-controlled clinical trials:

1- Definition of clinical trials

2- The purpose of clinical trials

3- Design of clinical trials (2 groups; study drug vs. placebo)

4- Placebo definition

5- Reasons to use placebos

6- Chance of receiving placebo (Randomization)

7- Placebos and life threating conditions

8- Ethical committee approval

9- Receiving other treatment and best of care besides placebos

10- Data and Safety Monitoring Committee (DSMB)

11- Chance to switch when the study drug is beneficial

12- The right to stop and discontinue the study

13- Expected benefits of participation in placebo-controlled clinical trials.

The language and the design of the pamphlet followed all the principles and strategies discussed earlier related to CLT. The booklet used simple and easy to understand language and avoided some trial-related terms such as "protocol" and "eligibility" that might be poorly understood. Some explanatory corresponding images were included to add further explanation to readers. For example, an image of the randomization process was added to help readers understand this term. At the end of the booklet, a summary of all the presented information was phrased in a different way to assure a reader's understanding. The spelling and grammar tool from Microsoft Word 2013 ® to describe the Flesch-Kincaid Grade Level Score was used to achieve a seventh-grade reading level score. The booklet was colored and produced on magazine-quality paper. The booklet was revised and pilot tested on few patients to improve readability and reduce ambiguity. A group of experts in clinical trials

reviewed the booklet and assessed its validity. An assistant professor (Brandi C. Fink, Ph.D.) in the field of clinical psychology from the University of New Mexico examined the educational booklet to validate the use of the CLT principles appropriately within the booklet. The assistant professor met one of the study researchers (K.F.M) and read about the study design, objectives and methods to have a better understanding about the study. Then the assistant professor examined the educational booklet to verify that all of the proposed CLT principles were incorporated within the booklet. The assistant professor validated and approved the educational booklet and no further changes were required.

2-The Educational Video:

The video was developed based on review of other similar clinical trial information materials as well as from the input from the study team. The 8-minute video was entitled" Learn More About Placebo Clinical Trials" and described the same information about placebo controlled clinical trials included in the booklet (Appendix B). The video presented and narrated by a student selected from the College of Pharmacy at the University of New Mexico. The narrator read from a pre-written script to assure accuracy of information presented. Some images were included in the video while the narration process to provide further explanation for some terms such as randomization. Similar to the booklet, a summary of all the presented information in the video was phrased in a different way to assure viewers understanding. The video was produced with the assistance of an expert in the field of video production. The video was revised and pilot tested on few patients to improve its quality. A group of experts in clinical trials reviewed the video and assessed its validity. An assistant

professor (Brandi C. Fink, Ph.D.) in the field of clinical psychology from the University of New Mexico examined the educational video to validate the use of the CLT principles appropriately within the video. The assistant professor met one of the study researchers (K.F.M) and read about the study design, objectives and methods to have a better understanding about the study. Then the assistant professor examined the educational video to verify that all of the proposed CLT principles were incorporated within the video. The assistant professor validated and approved the educational video and no further changes were required.

3- The Control Material:

Participants in the control group received only a standard consent form. The standard consent form covered regular information that is usually included in consent forms for clinical trials such:

1. Purpose of the New study drug
2. Procedures including randomization
3. Time duration of the procedures and study
4. Discomforts and risks
5. Potential benefits
6. Statement of confidentiality
7. Voluntary participation

Moreover, the only piece of information relevant to placebos in the standard consent form is the definition of placebos as they defined as “tablets that look like the study drug but without active substance”. The other common definition for placebos which is “sugar pills” was intentionally avoided because this definition was

mistakenly connected by some patients to diabetes.[63] Because the present study included diabetic patients, this definition was avoided.

Questionnaire Design:

The questionnaire was designed based on previous studies assessed patient knowledge, perceptions and their willingness to participate in placebo-controlled clinical trials. The questionnaire was seven pages long and was composed of seven different sections. These sections were:

1- Patient's perceived threat about his/her health
2- Patient's cognitive load related to the educational interventions
3- A scenario for a hypothetical placebo-controlled clinical trial
4- Patient's knowledge about placebo-controlled clinical trials
5- Patient's perception about placebo controlled clinical trials
6- Patient's willingness to participate in placebo-controlled clinical trials
7- Patient's characteristics section.

Section I: Patient's Perceived Threat Statements About his/her Health:

In this group of statements, there were two to three statements to represent a patient's perceived susceptibility and perceived severity. The first three statements measured the patient's perceived severity *"My kidney problem is serious.", "I face more life difficulties because of my kidney problem"* and *"My family faces more life difficulties because of my kidney problem*". The other two statements measured patient's perceived susceptibility "*I worry that my kidney problem will get worse*" and "*I feel I may also get other diseases*". Participants responded to the previous statements by

selecting one of the following responses; Strongly Agree (SA), Agree (A), Somewhat Agree (SWA), Disagree (D), Somewhat Disagree (SWD) and Strongly Disagree (SD).

Section II: Patient's Cognitive Load:

This section measured the patient's cognitive load caused by reading or watching the educational material. Because this section is relevant to the educational materials, it was only included in the questionnaires administered to the participants in the interventional groups. Two levels of cognitive load were measured, the mental effort level and the difficulty level. For the mental effort, there was one question that asked patients to rate their level of mental effort; "*In reading/watching the educational material I used*" with a response of a 7-point scale ranging from +3 (extremely low mental effort) to -3 (extremely high mental effort).[64] For the difficulty level, there was one question that asked patients to rate the difficulty level of the educational materials "*How easy or difficult was this educational material to understand*" with a response of a 7-point scale ranging from 3 (extremely easy) to -3 (extremely difficult).[64]

Section III: Information of the offered hypothetical study (Standard consent form):

The hypothetical study was to assess the safety and efficacy of a hypothetical drug called "The new drug". The hypothetical study was a randomized, double blind placebo- controlled clinical trial. The information for the hypothetical study covered all the following aspects:

1. Purpose of the new drug
2. Procedures including randomization

3. Time duration of the procedures and study

4. Discomforts and risks

5. Potential benefits

6. Statement of confidentiality

7. Voluntary participation

Section IV: Patient's knowledge about Placebo Controlled Clinical Trials:

Under this part of the questionnaire, there were 10 true/false questions. Those questions were based on the information presented in the educational materials. The true/false format for those questions helped to assess a patient's knowledge about placebo controlled clinical trials. Table 8 lists all the 10 true/false questions.

Table 8: Section IV of the questionnaire; patient's knowledge about placebo-controlled clinical trials section

No.	The sentence	Correct answer
1	A placebo is a substance that looks like the study drug but with active drug in it	**X**
2	Most patients can easily tell if they are taking a placebo from the actual study drug	**X**
3	Randomization means that my treatment will be chosen by chance	√
4	Other than the study drug, patients in the placebo group will not get the same medical care as patients in the study drug group	**X**
5	There are ethical and scientific reasons to use placebos in clinical studies	√
6	The Institutional Review Board meets before a study begins to make sure that the rights and welfare of patients are protected	√
7	The Data Monitoring Board is responsible for stopping a clinical study if the study drug works better and more effective than the placebo	√
8	Placebos alone can be given to patients with serious medical conditions	**X**
9	You must not talk to others (family member or a friend) about the clinical study before making your decision whether or not to participate	**X**
10	You can withdraw at any time from clinical studies using placebos	√

Section V: Patient's Perceptions about Placebo Controlled Clinical Trials:

A patient's perception about placebo controlled clinical trials was the sum of patient's perceived barriers and patient's perceived benefits. There were 3 statements for a patient's perceived barriers and 3 statements for a patient's perceived benefits with a total of 6 statements. The statements for the perceived

barriers were: "*I am suspicious of placebo clinical trials", "Placebo clinical trials are not ethical"* and "*I am confident the group of people who approve placebo clinical trials make sure all participants are treated fairly*". The patient's perceived benefits statements were: "*There may be benefits for me if I participate in a placebo clinical trial", "I will still get the best medical care even if I participated in placebo clinical studies"* and "*There may be benefits for other people like me if I participate in a placebo clinical trial*". Participants responded to the statements by selecting one of the following responses; Strongly Agree (SA), Agree (A), Somewhat Agree (SWA), Disagree (D), Somewhat Disagree (SWD) and Strongly Disagree (SD).

Table 9. The HBM components and their relevant to the questionnaire items.

HBM Component	Definition	Relevant Likert statement or application in the questionnaire
Perceived Severity	Patient's concerns about the seriousness of a condition or illness.	1- My kidney problem is serious. 2- I face more life difficulties because of my kidney problem. 3- My family faces more life difficulties because of my kidney problem.
Perceived Susceptibility	Patient's beliefs about their risk for getting a condition	4- I worry that my kidney problem will get worse. 5- I feel I may also get other diseases.
Perceived Barriers	Identify patient's concerns or negative beliefs about a health behavior	6. I am suspicious of placebo clinical trials 7.Placebo clinical trials are not ethical 8. I am confident the group of people who approve placebo clinical trials make sure all participants are treated fairly
Perceived Benefits	Patient's belief related to the outcomes of a certain behavior to reduce their susceptibility to or severity of an illness	9. There may be benefits for me if I participate in a placebo clinical trial 10. I will still get the best medical care even if I participated in placebo clinical studies 11. There may be benefits for other people like me if I participate in a placebo clinical trial
Cues to Action	A stimulus that can trigger appropriate health behavior	Educational booklet or Educational video
Self-Efficacy	Patient's confidence to adopt a behavior or take action	Patient's previous participation in a clinical trial (YES/NO)

Section VI: Patient's Willingness to Participate in Clinical Trials Statements:

This section measured patient's willingness to participate in placebo-controlled clinical trials using six different scenarios. Patients were asked to answer the following questions:

Scenario 1 (main scenario): After you have read about the "New Drug" study, how likely would you join the study?

Scenario 2: If the study had 2/3 of the patients get the New Drug plus usual medications and 1/3 of patients get the placebo plus usual medications, how likely would you join the New Drug study?

Scenario 3: If the study had 3/4 of the patients get the New Drug plus usual medications and 1/4 of patients get the placebo plus usual medications. How likely would you join the New Drug study?

Scenario 4: If the study was done for a short time (one month) instead of a year, and half of the patients got the study drug "The New Drug" alone without taking your usual medications and the other half of patients take placebo alone without taking usual medications, how likely would you join the New Drug study?

Scenario 5: If the was done for a short time (one month) instead of a year and 2/3 of the patients got the "New Drug" alone without taking your usual medications and 1/3 of patients take placebo alone without taking usual medications, how likely would you join the New Drug study?

Scenario 6: If the study was done for a short time (one month) instead of a year and 3/4 of the patients the study drug "The New Drug" alone without taking your usual medications and 1/4 of patients take placebo alone without taking usual medications,

how likely would you join the New Drug study?

Patients responded to the previous six questions by selecting one of the following responses: High Unlikely, Unlikely, Somewhat Unlikely, Undecided, Somewhat Likely, Likely and High Likely. Lastly, patients were asked to provide their reasons to accept or to refuse the participation in the offered trial.

Section VII: Patient's Characteristics Section:

This section collected patients' characteristics such as age, gender, educational level, socioeconomic status and previous participation in clinical trials. This section represented the component of self-efficacy and the modifying factors in the HBM model.

Questionnaire Pretesting and Other Considerations:

The questionnaire was pilot tested on 5 patients to establish face validity. During the face validity phase, the questionnaire was tested to assure readability, comprehension of instructions, and clarity. Based upon feedback from patients, minor modifications were made to the questionnaire to eliminate any ambiguous phrasing.

In this present study, the 7-point Likert scale was used because it provides more accurate measure of a participant's true evaluation as well as higher reliability and validity results.[65-67] Moreover, the inclusion of the word "Strongly" on the response options was to increase the intensifying effect while the inclusion of the word "Somewhat" was to decrease the overlap of answers.[65] We also included a midpoint response (neutral option) in the scale because we believe it is considered

as a valid response for the present study as well as it increased the validity and reliability of the questionnaire.[65]

Other best practices with regard to paper-based questionnaire design have been considered.[68] For instance, statements were as short as a possible to increase respondents' comprehension. Also, closed-ended questions were used to shorten the length of the questionnaire and therefore, to reduce the respondents' burden. The patients' characteristics section was placed at the end of the questionnaire in order to avoid negative feelings about the provision of personal information impacting on the perceptions or participation in the study.[65] Copies of the different questionnaire forms are available in appendices C-F.

Sample Size Estimation:

The sample size was estimated based on the results of a pilot study conducted by Campbell et al. [10] to assess patients' knowledge after reading a handbook about clinical trials. Patients who reviewed the educational handbook had a knowledge score of 84.5% with a standard deviation of ±1.7% compared to 64.4% with a standard deviation of ±4.3% for the control group.[10] This gives a mean difference of 20.1% between the two groups. To be more conservative in estimating the sample size for the present study, the difference in the means between the groups was lowered to 10% and the standard deviation within the groups was increased to 10%. Using alpha level of 0.05, a sample size of 27 participants per group (total= 108) was required to achieve 85% statistical power. Table 10 shows different sample sizes using different levels of standard deviation, mean difference and statistical power.

Table 10: Estimation of sample size sample sizes using different levels of standard deviation, mean difference and statistical power

Standard Deviation	6			8			10		
Mean difference/ Power	**5**	**10**	**15**	**5**	**10**	**15**	**5**	**10**	**15**
.80	34	9	5	60	16	8	95	24	11
.85	38	10	5	67	18	8	105	27	13
.90	34	12	6	76	20	10	120	30	15

Randomization Process and Patients Assignment to Study Groups:

The study participants were randomized to one of the four groups; the educational booklet, the educational video, both interventions or the standard consent form. Stratified randomization was used in this study to ensure that patients' characteristics are balanced between the four groups. Two main patient characteristics were used in the randomization process, gender (male or female) and age group (less than 50 and 50 or greater years old). As a result, there were 4 strata to match patients with during the randomization process. Thereafter, using a block size of four and allocation ratio of 1:1:1:1 for each group, the number of blocks per stratum was calculated and the randomization assignment numbers were generated. Table 11 shows the number for each stratum and the required number of randomization blocks.

Table11. Number of patients for each stratum and for each randomization block

Number of participants according to gender (%)	Number of participants per age group (%)	Number of blocks per stratum (Block size=4)
Males: 54(50)	Less than 50: 27 (50) 50 or greater: 27 (50)	7 7
Females: 54(50)	Less than 50: 27 (50) 50 or greater: 27 (50)	7 7

Educational Interventions and Questionnaire Administration and Collection:

In each selected clinic and with the help of the clinic staff, a study researcher (K.F.M) approached patients as they were checking in before or checking out after their physician visit. Patients were given an introduction to the study and then asked to participate. The informed consent was obtained from those patients who agreed to participate. The study researcher then collected gender and age of the participant in order to allocate the participant into the matching stratum. Thereafter, the study researcher followed the randomization assignment of that stratum to administer the questionnaire to the participant and the intervention.

Participants were encouraged to take the time they needed when reading or watching the intervention as well as if they needed to read or watch the intervention more than once. For participants who watched the video, earphones were provided to maximize the quality of listening to the video. Upon the completion of reading or watching the intervention, participants were instructed to complete the questionnaire and then return it to the study researcher upon full completion.

In order to avoid selecting the same patient during the study period, medical record numbers for participants were obtained from the clinic staff and used as a reference list when selecting the next participant within the three clinics. Participants were offered a $5 gift card after data collection was completed as an incentive for their time and participation in the survey. All hard copies of the completed questionnaires were stored in the researcher's locked office and will be properly destroyed after completion of the study.

Statistical Analyses:

Descriptive statistics for all the collected demographic characteristics within the four groups were compared using ANOVA for continuous data and chi-square test for categorical data. The data collected from the different sections of the questionnaire were analyzed as the following:

Section I: Patient's Perceived Severity and Susceptibility:

Points were given for each response ranging from +3 for (Strongly Agree) to -3 for (Strongly Disagree). The mean scores for the perceived severity (3 statements) and the mean score for the perceived susceptibility (2 statements) for each group were calculated. For the comparison between the groups, data collected from Likert statements were treated as interval data, therefore, one-way analysis of variance (ANOVA) was used. If significant difference was found, Tukey's Honestly Significant Difference (HSD) multiple comparison procedure was used to assess the difference between each pair of randomized groups.[69-71]

Section II: Patient's Knowledge about Placebo-Controlled Clinical Trials:

Comparisons between the groups regarding overall knowledge scores (% correct) was analyzed using ANOVA. If significant difference was found, Tukey's Honestly Significant Difference (HSD) multiple comparison procedure was used to assess the difference between each pair of the randomized groups.

To compare the responses for each knowledge question, chi-square test was used or the Fisher's exact when values within specific cells were small (<5).

Section III: Patients' Perceptions about Placebo-Controlled Clinical Trials (Perceived Barriers and Benefits):

For the first two statements for the perceived barriers statements; *"I am suspicious of placebo clinical trials"* and *"Placebo clinical trials are not ethical"* points were given for each sentence ranging from +3 for (Strongly Disagree) to -3 for (Strongly Agree). For the remaining statements, points were given for each sentence ranging from +3 for (Strongly Agree) to -3 for (Strongly Disagree). The mean score for the perceived barriers (3 statements) and the mean score for the perceived benefits (3 statements) for each group were calculated. For the comparison between the groups, data collected from Likert statements were treated as interval data, therefore, ANOVA was used. If significant difference was found, Tukey's Honestly Significant Difference (HSD) multiple comparison procedure was used to assess the difference between each pair of randomized groups.[69-71] A further comparison for each statement individually between the groups was conducted using nonparametric Kruskal Wallis tests.

Section IV: Patient's Willingness to Participate in Clinical Trials Statements:

The statistical analysis for this section was conducted after categorizing the responses for each questions to a dichotomous response; Yes, or No. Patients with the responses of Somewhat Likely, Likely and High Likely were categorized as Yes. On the contrary, patients with the responses of Undecided, Somewhat Unlikely, Unlikely and High Unlikely were categorized as No. For each question, responses were assessed using chi-square test or the Fisher's exact when values within specific cells were small (<5).

Significant Predictors for Willingness to Participate in placebo Controlled Clinical Trials:

The statistical analysis for this section was conducted after categorizing the responses for each questions to a dichotomous response; Yes, or No. Patients with the responses of Somewhat Likely, Likely and High Likely were categorized as Yes. On the contrary, patients with the responses of Undecided, Somewhat Unlikely, Unlikely and High Unlikely were categorized as No. A patient's demographics, patient's knowledge score, patient's perceived severity score, patient's perceived barriers score and the type of intervention were examined as possible predictors for the willingness to participate in placebo-controlled clinical trials. Moreover, the Variance Inflation Factor (VIF) was calculated to detect if two or more predictor variables in the model were highly correlated.[72]

Other Statistical Considerations:

The questionnaire reliability and validity had been assessed in previous studies.[10,73,74,75] Missing responses in Likert statements will be replaced by the same item mean from all the individuals who responded to the same item within the same study group. A priori significance level of $p < 0.05$ is considered to be statistically significant and all the analyses were performed using the statistical software (SPSS).

Study Approval:

Prior starting the study, an approval letter from the Human Research Protection Office within the University of New Mexico under the expedited review process was obtained as the questionnaire was anonymous and there were no known risks involved with participating with the study (Appendix G).

Results of Pilot Testing:

The questionnaire was pilot tested using five patients who agreed to participate in this study. Patients were asked to identify for any problems with the wording of the item, response options and instructions of the questionnaire. Patients were also asked to assess the layout and print size of the questionnaire. Patients were asked to provide any suggestions to improve the questionnaire. There were no major changes on the questionnaire. One minor change was added to the questionnaire. This change was to add the word "Hypothetical" to title of study background in section 3 to be read as: "Hypothetical Study Background". Table 12 depicts all patients' characteristics and the results of the pilot test.

Table 12. Pilot test results for the questionnaire

Patient characteristic and Questions	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age and gender	58 – M*	46- F*	57- F*	55- F*	57 –F*
Were the questions in the survey clear?	Yes	Yes	Yes	Yes	Yes
Were the instructions in the survey clear?	Yes	Yes	Yes	Yes	Yes
Were there any problems with font size/ print size?	No	No	No	No	No
Time to complete the survey (Minute: Second)	6:25	5:44	7:43	8:05	13:46

*M: Male, F: Female

CHAPTER 4

RESULTS

Introduction

This chapter presents the study results. The first part of this chapter presents patients' demographics for the overall study sample followed by patients' demographics for each study group. The second part presents the results according to the study primary and secondary objectives. Lastly, study results are presented according to each clinic in the study.

Patients' Demographics for the Overall Study Sample:

One hundred and eight patients participated in our study. There were 27 participants in each group. Fifty-six patients were females (53.4%) and 52 patients were males (46.6%). Male participants had an average age of 57.73 years (±12.23) while female participants had an average age of 55.02 years (±11.92). The average age for the overall study sample was 56.32 years (±12.03). The oldest participant was an 83-year-old female. The youngest participants were one female and one male aged 23 years old,

The majority of the study participants identified themselves as Hispanic (n=41, 38%) followed by Non-Hispanic whites (n=39, 36.1%), African American (n=7, 6.5%), and other (n=21, 19.4%). Previous participation in a clinical trial was reported by 30 patients (27.8%); 7 patients had participated in a placebo controlled clinical trial. There was no significant difference among in patients' characteristics among the study groups. This indicates that the randomization process was successful. Table 13 depicts all patients' characteristics among the study groups.

Table 13. Baseline characteristics for study participants: n(%)

Patient characteristic / study group	The Booklet n=27	The video n=27	The booklet and video n=27	The control n=27	P value
Age (mean ± SD)	57.33 (11.07)	52.70 (10.74)	56.63 (12.62)	58.63 (13.57)	0.31
Gender					
Male	13 (48.1)	13 (48.1)	13 (48.1)	13 (48.1)	1.00
Female	14 (51.9)	14 (51.9	14 (51.9	14 (51.9	
Race					
Non-Hispanic White	12 (44.4)	9 (33.3)	8 (29.6)	10 (37)	
Hispanic	9 (33.3)	12 (44.4)	10 (37)	10 (37)	
African American	3 (11.1)	3 (11.1)	0 (0.0)	1 (3.7)	0.35
Other	3 (11.1)	3 (11.1)	9 (33.3)	6 (22.2)	
Education					
Less than high school	1 (3.7)	1 (3.7)	1 (3.7)	2 (7.4)	
High school	9 (33.3)	10 (37)	10 (37)	11 (40.7)	0.67
College	7 (25.9)	11 (40.7)	11 (40.7)	11 (40.7)	
Graduate	10 (37)	5 (18.5)	5 (18.5)	3 (11.1)	
Marital status					
Single	4 (14.8)	10 (37)	9 (33.3)	11 (40.7)	
Married	14 (51.9)	12 (44.4)	13 (48.1)	11 (40.7)	0.63
Divorce	7 (25.9)	4 (14.8)	4 (14.8)	5 (18.5)	
Widowed	2 (7.4)	1 (3.7)	1 (3.7)	0 (0.0)	
Income					
< $10,000	5 (18.5)	7 (25.9)	7 (25.9)	9 (33.3)	
$ 10,000 - < $ 25,000	10 (37)	10 (37)	10 (37)	9 (33.3)	
$ 25,000 - < $ 40,000	6 (22.2)	3 (11.1)	4 (14.8)	6 (22.2)	0.87
$ 40,000 - < $ 55,000	2 (7.4)	1 (3.7)	1 (3.7)	2 (7.4)	
> $ 55,000	4 (14.8)	6 (22.2)	5 (18.5)	1 (3.7)	
Previous Participant in a clinical study					
Yes	8	6	7	9	
No	19	21	20	18	0.82

Patients' Demographics according to study groups:

1. The Booklet Group:

Fourteen females (51.9%) and 13 males (49.1%) were randomized to the booklet group. The average age of the group was 57.33 years (±11.07) with a range from 23 to 75 years of age. Twelve participants (44.4%) reported themselves as Hispanic, 9 (33.3%) as Non-Hispanic White, 3 (11.1%) as African American and 3 (11.1%) as Other. Ten participants (37%) had a graduate degree, 7 (25.9%) with a college degree, 10 (33.3%) with high school degree and 1 (3.7%) with less than high school degree. Eight patients (29.6%) had previously participated in a clinical trial; 2 patients had participated in placebo controlled clinical trials.

2. The Video Group:

Twenty-seven participants were randomized to the video group in which females (51.9%) and 13 males (49.1%). The average age of the group was 52.7 years (±10.74). The oldest participant was 67 years old and the youngest was 26 years old. Twelve participants (44.4%) reported themselves as Hispanic, 9 as Non-Hispanic white (33.3%), 3 as African American (11.1%) and 3 (11.1%) as Other. Five participants (18.5%) had a graduate degree, 11 (40.7%) with a college degree, 10 (37%) with high school degree and 1 (3.7%) with less than high school degree. Six patients (22.2%) had previously participated in a clinical trial; one patient had participated in a placebo controlled clinical trial.

3. The Booklet and Video Group:

Fourteen females (51.85%) and 13 males (49.15%) were randomized to the booklet and the video group. The average age of the group was 56.63 years (±12.62)

ranging from 25 to 82 years old. Eight participants (29.6%) reported themselves as Hispanic, 10 as Non-Hispanic white (37%) and 9 (33.3%) as Other. Five participants (18.5%) had a graduate degree, 11 (40.7%) with a college degree, 10 (37%) with high school degree and 1 (3.7%) with less than high school degree. Seven patients (25.9%) had previously had participated in a clinical trial, 2 patients had participated a placebo controlled clinical trial.

4. The Control Group:

Similar to the other groups, 14 (51.85%) and 13 males (49.15%) were randomized to the control group. The average age of the group was 58.63 years (±13.57). Ten participants (37%) reported themselves as Hispanic, 10 as Non-Hispanic white (37%), 1 as African American (3.7%) and 6 (22.2%) as Other. Three participants (18.5%) had a graduate degree, 11 (40.7%) with a college degree, 11 (40.7%) with high school degree and (7.4%) with less than high school degree. Nine patients (33.3%) had previously participated in a clinical trial; 2 patients had participated a placebo controlled clinical trial.

Patients' Perceived Threats:

Results under this section range from -3 to +3 points where the higher the score the more perceived severity and susceptibility.

1. Patients' Perceived Susceptibility:

Patients in the control group had the highest perceived susceptibility score of 0.92 (±1.39) out of 3 points. Patients in the booklet and video group had the lowest perceived susceptibility score of 0.51 (±1.41). Patients in the booklet group had a score of 0.88 (±1.45) while patients in the video group had a score of 0.81 (±1.44).

There was no significant difference among the different groups related to patients' perceived susceptibility score (p= 0.71).

2. Patients' Perceived Severity:

Patients in the control group had the highest perceived severity score of 1.66 (±1.24), while patients in the video group had the lowest perceived severity score of 1.34 (±1.38). Patients in the booklet group had a score of 1.49 (±1.06) while patients in the booklet and video group had a score of 1.59 (±1.20). There was no significant difference among the different groups related to patients' perceived severity score (p= 0.78).

Primary Objective: Patients' Knowledge Score:

Patients in the booklet group had a knowledge score of 9.59 out of 10 possible points (±0.74). Patients in the video group and patients in the booklet and video group had a knowledge score of 9.66 (±0.55 and ±0.62 respectively), which was slightly higher than patients' score in the booklet group. Patients in the control group had the lowest knowledge score of 8.03 points (±1.84). There was a significant statistical difference in the knowledge score among the groups ($p < 0.01$). In the multiple comparisons test, all the three interventional groups had a significant statistical difference in comparison to the control group ($p < 0.01$). Among the three interventional groups, there was no significant statistical difference in patients' knowledge score. Table 14 shows the results for patients' knowledge score among the study groups.

Table 14. Patients' knowledge score according to study groups.

Study Group	Mean	Std. Deviation	Minimum	Maximum	P Value
Control	8.04	±1.40	4	10	
Booklet	9.59	±.74	7	10	
Video	9.67	±.55	8	10	**< 0.01**
Booklet and Video	9.67	±.62	8	10	

For the patients' knowledge score per individual questions, there was a significant difference between the interventional groups and the control group in six questions. These questions are question number 1,2,4,7,8 and 9. The highest frequency of incorrect answers were in the control group on question numbers 7 and 8. There were 12 incorrect answers for question number 7 and 10 incorrect answers for question number 8 which were the highest frequencies of incorrect answers among the four groups. Question 6 was answered correctly by all the participants in all the four groups. Table 15 show the individual questions and their corresponding results within the study groups.

Table 15. Numbers of wrong and correct answers for questions 1 to 10 for each study group.

Question Number	Control		Booklet		Video		Booklet and Video		P Value
	Correct	Wrong	Correct	Wrong	Correct	Wrong	Correct	Wrong	
1	19	8	26	1	25	2	26	1	**< 0.01**
2	23	4	26	1	27	0	27	0	**< 0.01**
3	23	4	26	1	26	1	26	1	**0.02**
4	21	6	26	1	27	0	25	2	**0.24**
5	24	3	26	1	27	0	27	0	**0.01**
6	27	0	27	0	27	0	27	0	---
7	15	12	22	5	23	4	25	2	**< 0.01**
8	17	10	26	1	25	2	25	2	**< 0.01**
9	23	4	27	0	27	0	26	1	**0.02**
10	25	2	27	0	27	0	27	0	0.10

Secondary Objectives:

Patients' Perceptions related to placebo-controlled clinical trials:

Results in this section range from -3 to +3 points. The higher score indicates a more positive perception with less barriers toward placebo controlled clinical trials. Similarly, the higher score in a patient's perceived benefits indicates more expected benefits and more positive perception towards placebo controlled clinical trials.

1. Patients' Perceived Barriers:

The educational materials used in the three interventional groups were able to increase patients' perceived barriers score toward placebo controlled clinical trials. Patients in the video group had the highest mean score for the perceived barriers perception with a mean score of 1.97 (±0.88) points. Patients in the booklet and video group had a mean score for perceived barriers of 1.95 (±0.69) points while participants in the booklet group had a mean score of 1.74 (±1.03) points. The lowest average score for perceived barriers was in the control group with a score of 0.87 (±1.11) points. There was a significant statistical difference among the four groups ($p<0.01$). In the multiple comparisons, all the three interventional groups had a significant statistical difference in comparison to the control group ($p < 0.01$). For the individual comparisons for the perceived barriers statements among the study groups, there was a statistical difference for the second statement "*Placebo clinical trials are not ethical"* among the four study groups ($p< 0.01$). The median score for the second statement for the three interventional groups was 2 (Agree) while the control group had a median of 0.00 (Neither agree nor disagree).

Table 16. Patients' perceived barriers score according to study groups.

Study Group	Mean	Std. Deviation	Minimum	Maximum	P Value
Control	0.87	1.11	-1.00	3.00	< **0.01**
Booklet	1.74	1.03	-1.33	3.00	
Video	1.97	0.88	.00	3.00	
Booklet and Video	1.95	0.69	0.67	3.00	

2. Patients' Perceived Benefits:

There was no statistical difference among the study groups related to patients' perceived benefits (p=0.37). Patients in the video group had the highest average score of 2.09 (±0.73) points. Patients in the booklet group had an average score of 2.00 (±0.73) followed by patients in the control group with an average score of 1.77 (±0.76). Lastly, patients in the booklet and video group had the lowest average score of 1.76 (±1.06). For the individual comparisons for the perceived benefits statements among the study groups, there was no statistical difference statements among the different groups.

Table 17. Patients' perceived benefits score according to study groups.

Study Group	Mean	Std. Deviation	Minimum	Maximum	P Value
Control	1.77	0.76	.00	3.00	0.37
Booklet	2.00	0.73	0.67	3.00	
Video	2.09	0.73	0.67	3.00	
Booklet and Video	1.76	1.06	-1.33	3.00	

Patients' Willingness to Participate in Placebo-controlled Clinical Trials:

Results under this section are presented after categorizing the responses of each question to a dichotomous response; Yes, or No. Patients with the responses of Somewhat Likely, Likely and High Likely were categorized as Yes. In contrast, patients with the responses of Undecided, Somewhat Unlikely, Unlikely and High Unlikely were categorized as No.

Results for Scenario 1: Allocation ratio of 1:1 for study drug to placebo plus standard of care:

Twenty (74.1 %) patients in the booklet group and 20 (74.1 %) patients in the video group said Yes to participate in the given study scenario. In the booklet and video group, there were 19 (70.4%) patients who said yes compared to 17 (63%) in the control group. There was no statistical difference among the four groups related to the number of patients who were willing to participate in the given study scenario (p=0.78).

Table 18. Number of patients willing to participate in scenario 1.

Study Group	Number of Accepters	Number of Decliners	P Value
Control	17	10	0.78
Booklet	20	7	
Video	20	7	
Booklet and Video	19	8	
Total	76	32	

Results for Scenario 2: Allocation ratio of 2:1 for study drug to placebo plus standard of care:

For each of the three interventional groups, 21 (74.1 %) patients said Yes to participate in the given study scenario. In the control group 18 (66.7%) patients accepted the given scenario. There was no statistical difference among the four groups related to the number of patients who were willing to participate in scenario 2 (p=0.72).

Table 19. Number of patients willing to participate in scenario 2.

Study Group	Number of Accepters	Number of Decliners	P Value
Control	18	9	0.72
Booklet	21	6	
Video	21	6	
Booklet and Video	21	6	
Total	81	27	

Results for Scenario 3: Allocation ratio of 3:1 for study drug to placebo plus standard of care:

In the video group, there were 23 (85.2%) patients who accepted to participate in this scenario. Twenty (74.1 %) patients in the booklet group and 20 (74.1 %) patients in the booklet and video group said Yes to participate in this scenario. The control group had only 18 (66.7%) accepters. There was no statistical difference among the four groups related to the number of patients who were willing to participate in this scenario (p=0.47).

Table 20. Number of patients willing to participate in scenario 3.

Study Group	Number of Accepters	Number of Decliners	P Value
Control	18	9	0.47
Booklet	20	7	
Video	23	4	
Booklet and Video	20	7	
Total	81	27	

Results for Scenario 4: Allocation ratio of 1:1 for study drug to placebo alone:

The booklet group had 10 (37%) patients accepted to participate in this scenario. Twelve (44.4%) patients in the video group and 12 (44.4%) patients in the control group were willing to participate in this scenario. The booklet and video group, however, had the highest number of patients who said "Yes" compared to the previous groups (n=14, 51.9%). Yet, there was no statistical difference among the four groups related to the number of patients who were willing to participate in this scenario (p=0.75).

Table 21. Number of patients willing to participate in scenario 4.

Study Group	Number of Accepters	Number of Decliners	P Value
Control	12	15	0.75
Booklet	10	17	
Video	12	15	
Booklet and Video	14	13	
Total	48	60	

Results for Scenario 5: Allocation ratio of 2:1 and placebo alone design:

The booklet group had 10 (37%) patients accepted to participate in this scenario. The video group had 12 (40.7%) patients and the control group had 13 (48.1%) patients accepted to participate in this scenario. Similar to the previous scenario, the booklet and video group, however, had more patients who said "Yes" compared to the previous groups (n=15, 55.6%). There was no statistical difference among the four groups related to the number of patients who were willing to participate in this scenario (p=0.53).

Table 22. Number of patients willing to participate in scenario 5.

Study Group	Number of Accepters	Number of Decliners	P Value
Control	13	14	0.53
Booklet	10	17	
Video	12	15	
Booklet and Video	15	12	
Total	59	49	

Results for Scenario 6: Allocation ratio of 3:1 and placebo alone design:

The booklet group had 9 (33.3%) patients accepted to participate in this scenario. The video group had 11 (40.7%) patients and the control group had 12 (44.4%) patients accepted to participate in this scenario. Similar to the previous scenario, the booklet and video group continued to have the highest number of accepters compared to the previous groups (n=15, 55.6%). There was no statistical difference among the four groups related to the number of patients who were willing to participate in this scenario (p=0.41).

Table 23. Number of patients willing to participate in scenario 6.

Study Group	Number of Accepters	Number of Decliners	P Value
Control	12	15	0.41
Booklet	9	20	
Video	11	16	
Booklet and Video	15	12	
Total	47	61	

Results for The Multiple Linear Regression Models:

This section presents results for the multiple linear regression models to predict patient's knowledge score, patient's perceived barriers score, and patient's perceived benefits score.

The Multiple Linear Regression Model for Patients' Knowledge Score:

The full multiple linear regression model was statistically significant to predict patients' knowledge score regarding placebo-controlled clinical trials ($p < 0.01$). The model included intervention type, clinic type, patient's perceived severity and susceptibility scores, patient's knowledge score, patient's perceived benefits and barriers scores, and other patient's characteristics such as education and income as possible predictors. The model showed that the predictors explained 54.3% of the variability of the dependent variable (patient's knowledge score). The model shows that the educational interventions were significant predictors for patients to score a higher knowledge score compared to the control group. For example, patients in the booklet group had a coefficient of 1.44 points in the knowledge score compared to the control group. Also, patients in the video group had a coefficient of 1.43 points in the knowledge score compared to the control group. Lastly, patients in the booklet and

video group had a coefficient of 1.53 points in the knowledge score compared to the control group.

Another significant predictor for patients' knowledge score was their annual income. Patients with an annual income of between $10,000 and $25,000 had 0.59 point more in knowledge score compared to patients with an annual income of less than $10,000 (p= 0.02). Moreover, patients with an annual income of between $40,000 and $55,000 had 0.94 point more in knowledge compared to patients with an annual income of less than $10,000 (p=0.04). In contrast, patient's perceived severity and susceptibility had a negative impact on a patient's knowledge score, however, they were not significant predictors. Table 24 shows all the predictors in the model and their impact on a patient's knowledge score.

Table 24. Predictors for patients' knowledge score

Variable	B Coefficient	P Value	VIF*
Clinic: Oncology (Ref.)	---	---	---
Diabetes	.103	.656	1.789
Kidney	-.030	.895	1.756
Intervention: Control (Ref.)	---	---	---
Booklet	**1.448**	**< 0.01**	1.687
Video	**1.430**	**< 0.01**	1.753
Booklet and Video	**1.531**	**< 0.01**	1.638
Perceived severity score	-.156	.072	1.599
Perceived susceptibility score	-.072	.382	2.017
Gender: Female (Ref.)	---	---	---
Male	-.069	.711	1.294
Age	-.006	.414	1.332
Race: Non-Hispanic White (Ref.)	---	---	---
Hispanic	-.050	.825	1.798
African American	-.347	.392	1.493
Other	-.377	.148	1.580
Education: Less than high school (Ref.)	---	---	---
High School	.266	.572	7.747
College	.464	.337	8.171
Graduate degree	.201	.706	7.137
Income: < 10,000	---	---	---
10,000 - < 25,000	**.596**	**.020**	2.213
25,000 - < 40,000	-.004	.990	1.882
40,000 - < 55,000	**.947**	**.041**	1.663
> 55,000	.669	.078	2.701
Previous participation in clinical trial: No (Ref.)	---	---	---
Yes	.232	.241	1.173

* VIF: Variance Inflation Factor

The Multiple Linear Regression Model for Patients' Perceived Barriers Score:

The full multiple linear regression model was statistically significant to predict patients' perceived barriers score regarding placebo-controlled clinical trials ($p < 0.01$). The model showed that the predictors explained 34.8% of the variability of the dependent variable (patient's perceived barriers score). The video intervention was a significant predictor with a coefficient of 1.02 points in a patient's perceived score compared to patients in the control group ($p < 0.01$). Similarly, the booklet and video intervention was a significant predictor with a coefficient of .85 point compared to patients in the control group ($p < 0.01$). The booklet intervention was not a significant predictor for patients' perceived barriers score with a coefficient of 0.53 point ($p=0.10$).

Moreover, a patient's knowledge score was not a significant predictor with a coefficient of 0.19 point ($p=0.10$). This means that for every one-point increase in a patient's knowledge score there was a 0.19 point increase in the perceived barriers score. Also, patients with previous participation in a clinical trial had a 0.30-point increase in the perceived barriers score compared to naive patients ($p=0.16$). Table 25 shows all the predictors in the model and their impact on a patient's perceived barriers score.

Table 25. Predictors for patients' perceived barriers score

Variable	B Coefficient	P Value	VIF*
Clinic: Oncology (Ref.)	---	---	---
Diabetes	-.126	.624	1.793
Kidney	-.037	.885	1.757
Intervention: Control (Ref.)	---	---	---
Booklet	.531	.100	2.372
Video	**1.026**	**< 0.01**	2.421
Booklet and Video	**.858**	**< 0.01**	2.403
Knowledge	.196	.103	2.189
Perceived severity score	-.011	.914	1.660
Perceived susceptibility score	.040	.665	2.035
Gender: Female (Ref.)	---	---	---
Male	-.007	.974	1.297
Age	.006	.502	1.343
Race: Non-Hispanic White (Ref.)	---	---	---
Hispanic	.003	.990	1.799
African American	-.666	.141	1.505
Other	.075	.795	1.619
Education: Less than high school (Ref.)	---	---	---
High School	-.617	.237	7.775
College	-.413	.442	8.259
Graduate degree	.243	.680	7.149
Income: < 10,000	---	---	---
10,000 - < 25,000	.053	.853	2.355
25,000 - < 40,000	.290	.373	1.882
40,000 - < 55,000	.501	.337	1.745
> 55,000	-.602	.158	2.800
Previous participation in clinical trial: No (Ref.)	---	---	---
Yes	.305	.167	1.192

* VIF: Variance Inflation Factor

The Multiple Linear Regression Model for Patients' Perceived Benefits Score:

The full multiple linear regression model for patients' perceived benefits score was not statistically significant (p =0.45, R^2= 19.2%). Although it was not a significant predictor, but the video intervention had the highest coefficient of 0.52 point among the other interventions (p=0.07). The booklet intervention had a coefficient of 0.25(p= 0.37) while the booklet and video intervention had a coefficient of 0.03 (p=0.81).

Previous participation in clinical trials was a significant predictor for patient's perceived benefits score with a coefficient of 0.41 point compared to naive patients (p=0.03). Table 26 shows all the predictors in the model and their impact on patients' perceived barriers score.

Table 26. Predictors for patients' perceived benefits score

Variable	B Coefficient	P Value	VIF*
Clinic: Oncology (Ref.)	---	---	---
Diabetes	.229	.319	1.793
Kidney	-.108	.635	1.757
Intervention: Control (Ref.)	---	---	---
Booklet	.254	.377	2.372
Video	.527	.071	2.421
Booklet and Video	.039	.891	2.403
Knowledge	.025	.813	2.189
Perceived severity score	.088	.314	1.660
Perceived susceptibility score	-.088	.283	2.035
Gender: Female (Ref.)	---	---	---
Male	-.233	.206	1.297
Age	.004	.594	1.343
Race: Non-Hispanic White (Ref.)	---	---	---
Hispanic	.024	.913	1.799
African American	-.591	.144	1.505
Other	-.052	.841	1.619
Education: Less than high school (Ref.)	---	---	---
High School	-.395	.397	7.775
College	-.698	.148	8.259
Graduate degree	-.483	.359	7.149
Income: < 10,000	---	---	---
10,000 - < 25,000	.188	.465	2.355
25,000 - < 40,000	.495	.091	1.882
40,000 - < 55,000	.810	.084	1.745
> 55,000	-.121	.751	2.800
Previous participation in clinical trial: No (Ref.)	---	---	---
Yes	**.418**	**.036**	1.192

* VIF: Variance Inflation Factor

Normality Assumptions:

The normality assumptions for the residuals were examined for the previous three models related to a patient's knowledge, patient's perceived barriers and patient's perceived benefits scores. Results from the normality plots for the three models showed that the residuals were normally distributed (Figure 11-19).

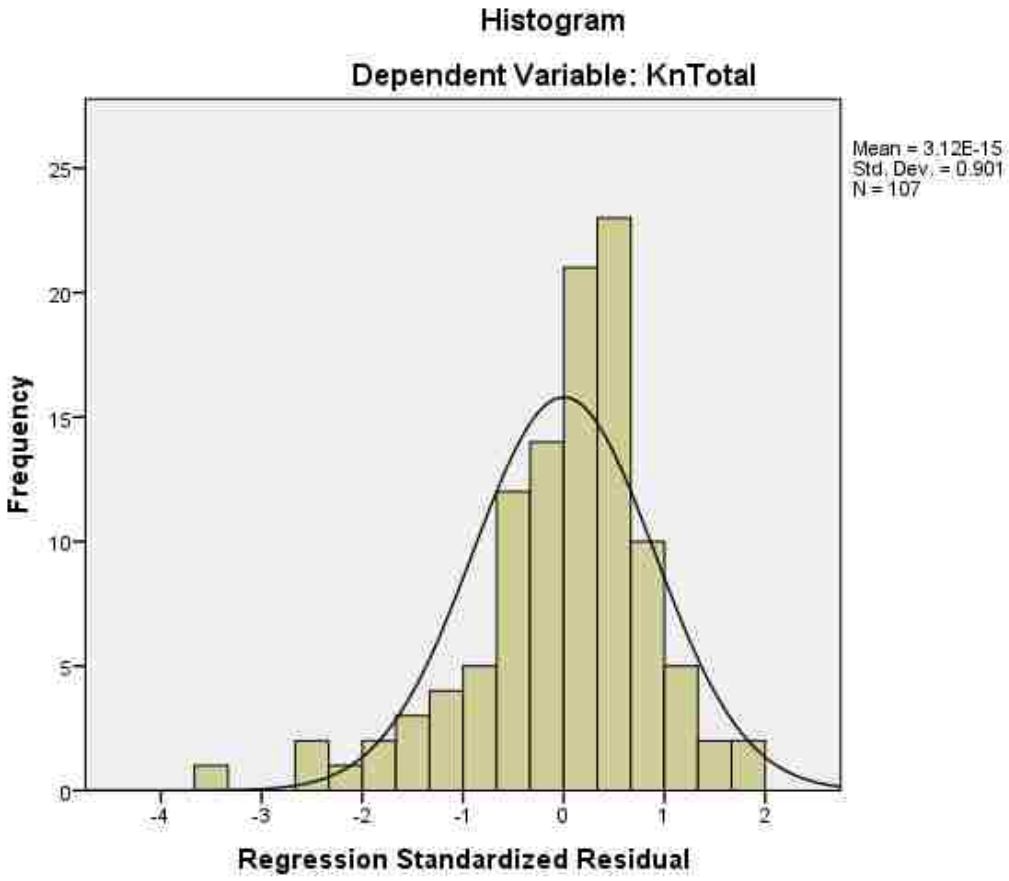


Figure 11. The standardized normal probability plot for residuals (Dependent variable: Patient's knowledge score)

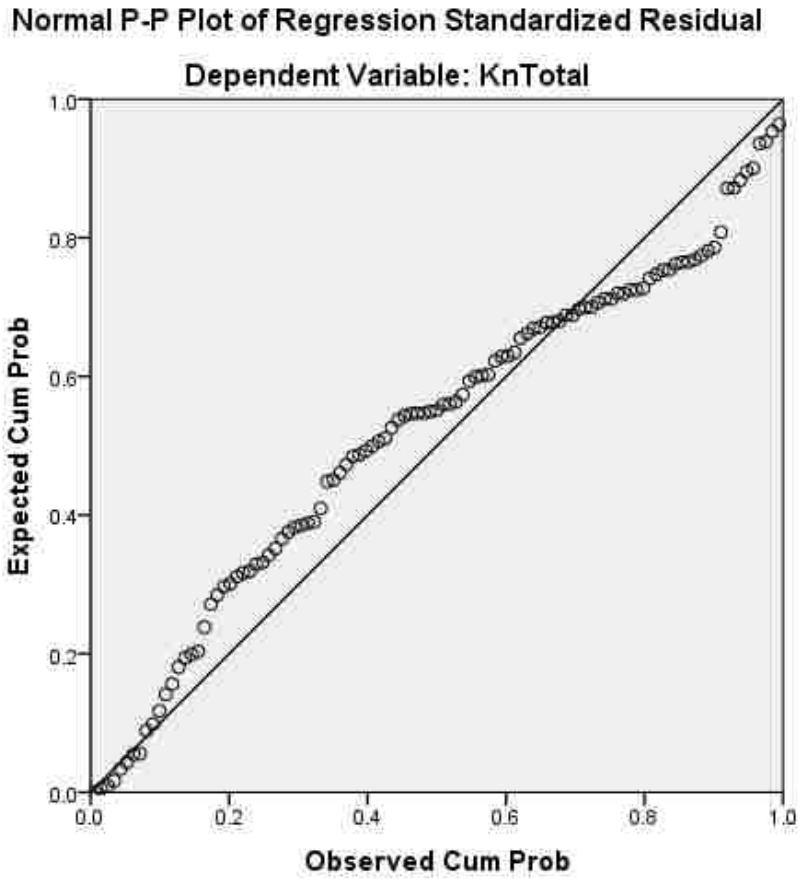


Figure 12. The standardized normal probability plot for residuals (Dependent variable: Patient's knowledge score)

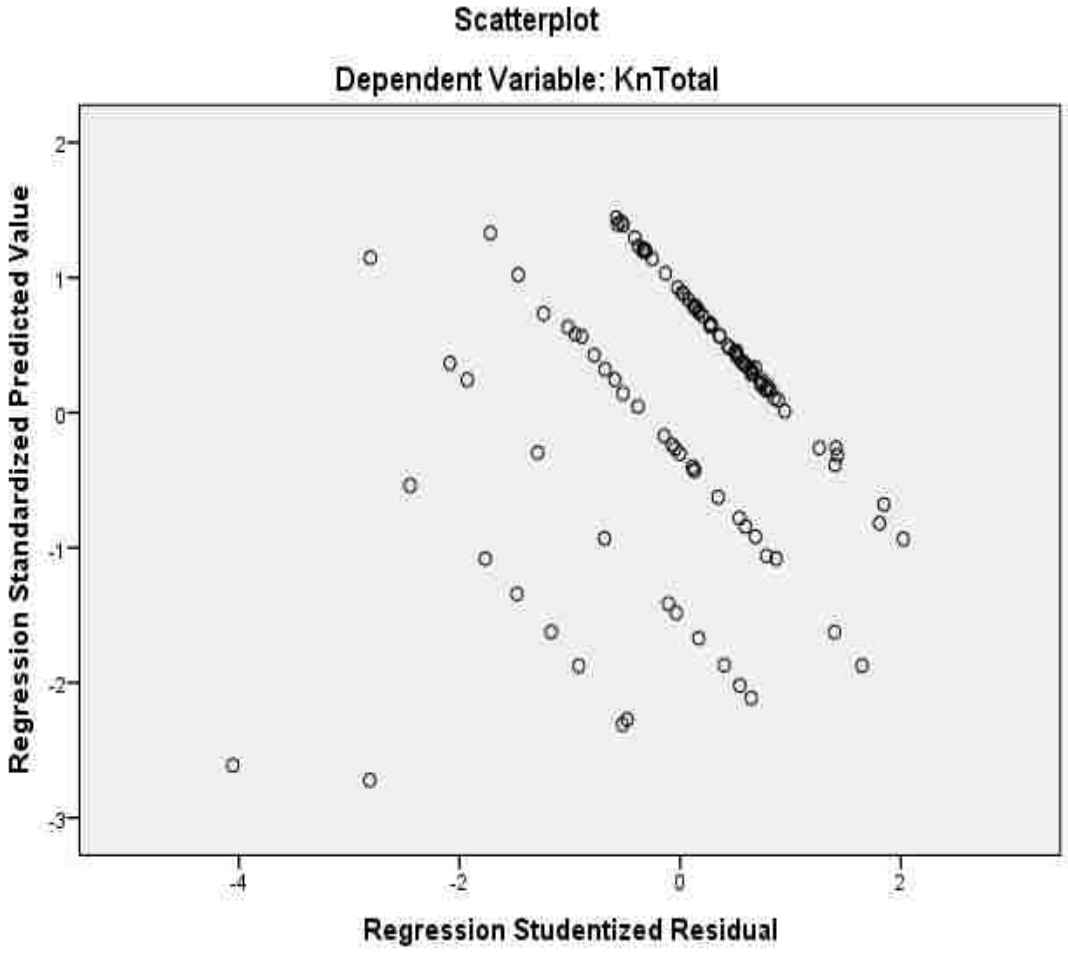


Figure 13. The scatter plot for residuals (Dependent variable: Patient's knowledge score)

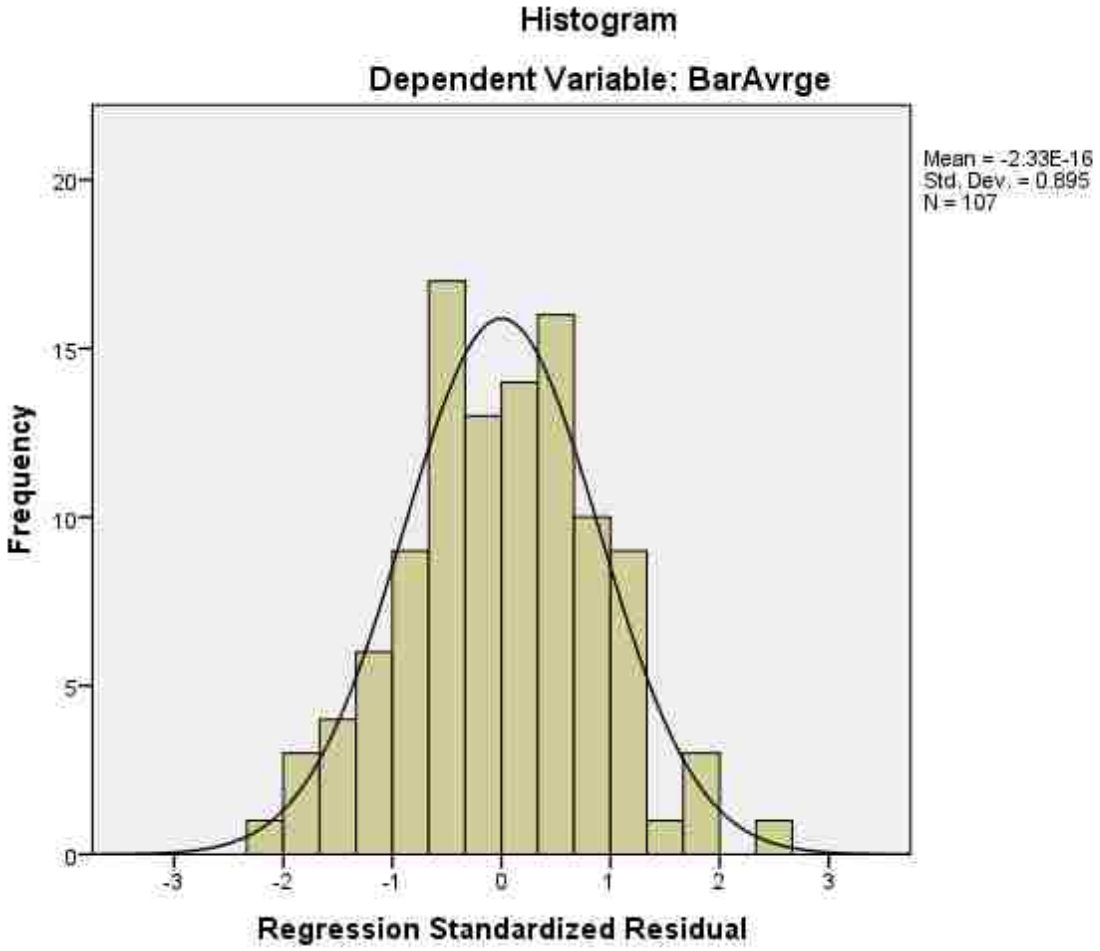


Figure 14. The standardized normal probability plot for residuals (Dependent variable: Patient's perceived barriers score)

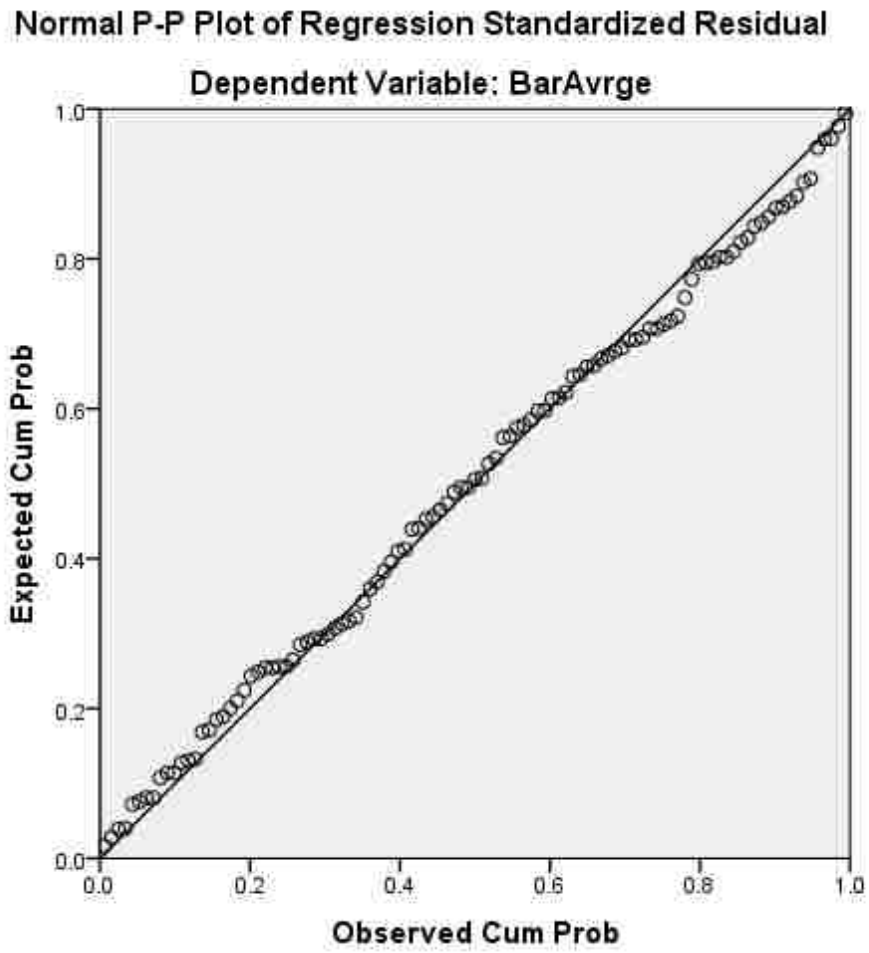


Figure 15. The standardized normal probability plot for residuals (Dependent variable: Patient's perceived barriers score)

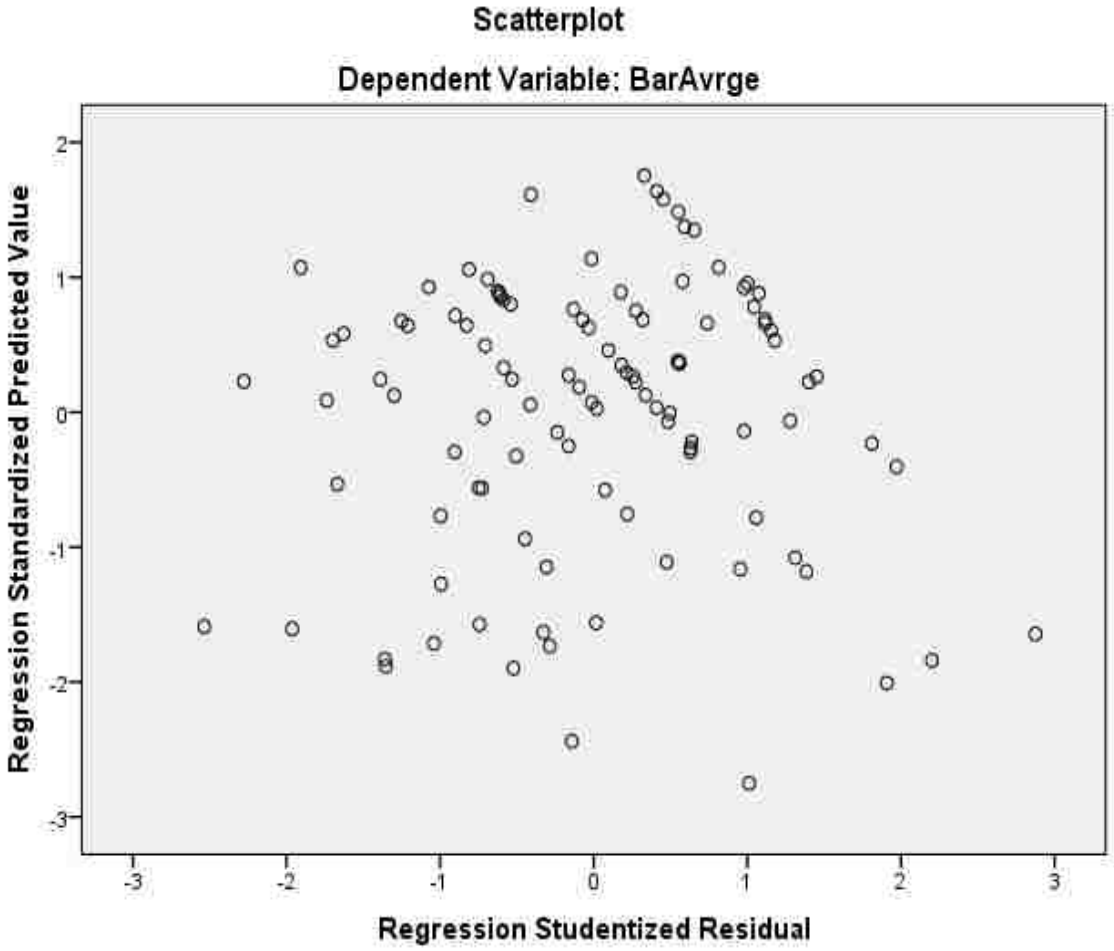


Figure 16. The scatter plot for residuals (Dependent variable: Patient's perceived barriers)

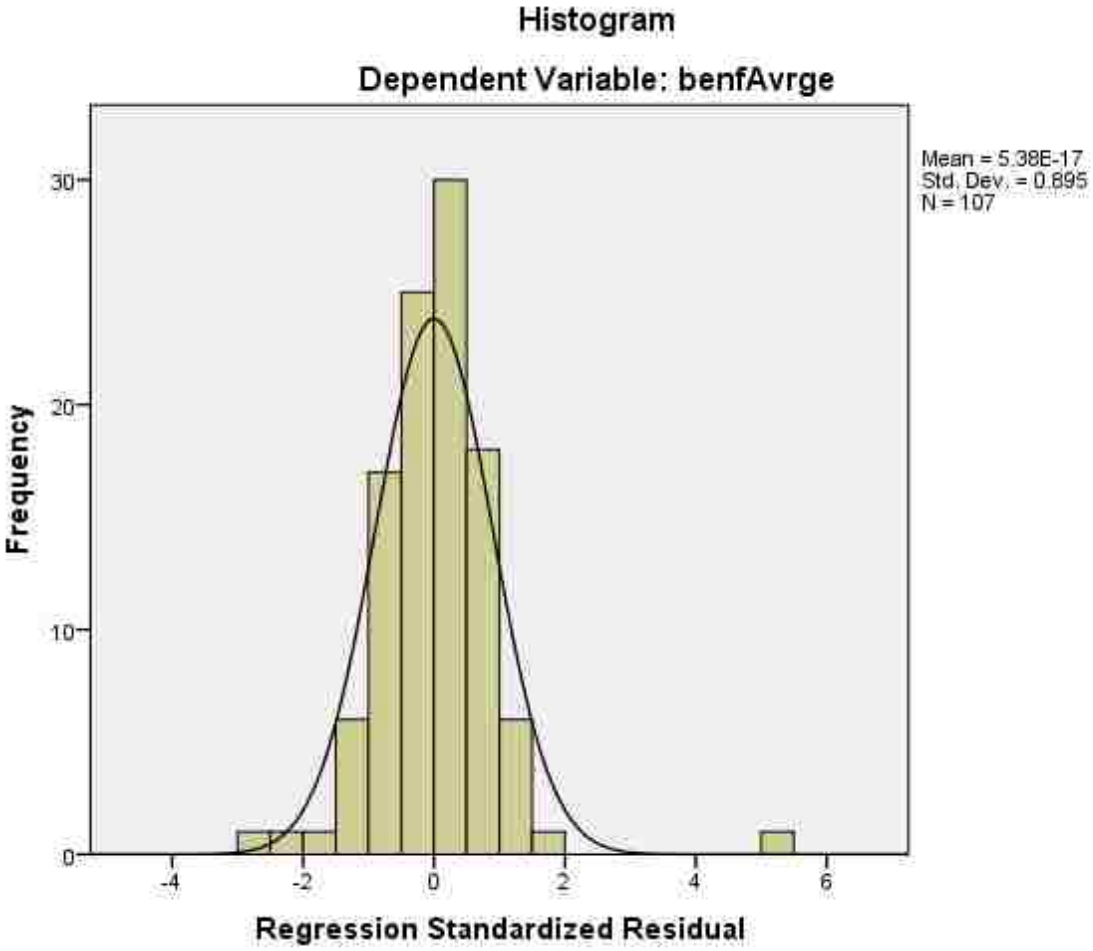


Figure 17. The standardized normal probability plot for residuals (Dependent variable: Patient's perceived benefits score)

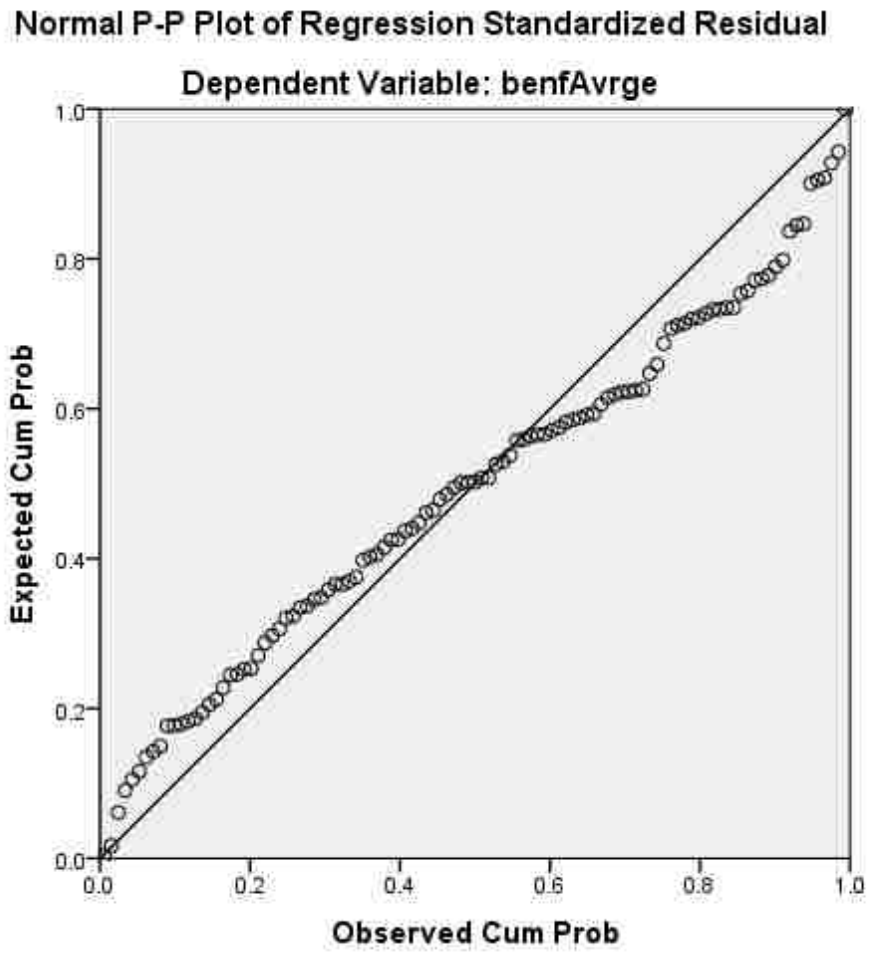


Figure 18. The standardized normal probability plot for residuals (Dependent variable: Patient's perceived benefits score)

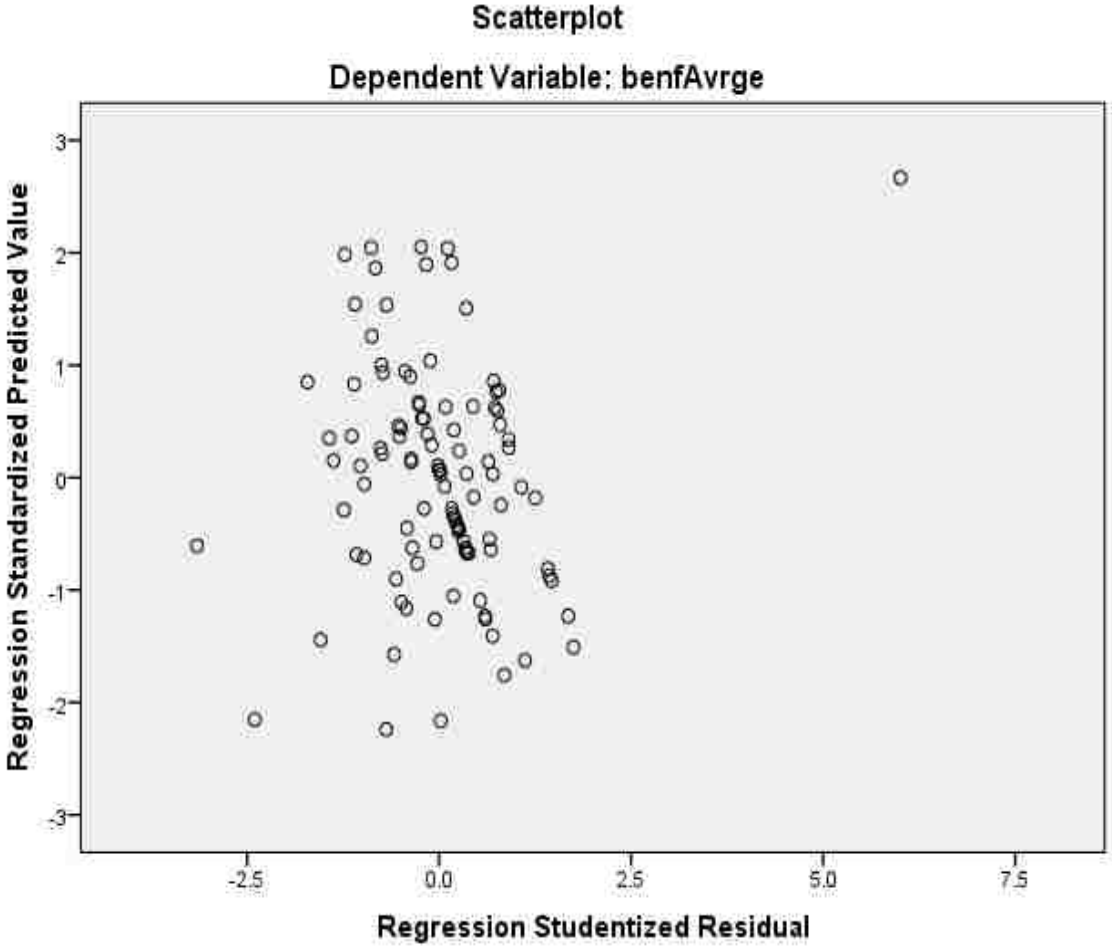


Figure 19. The scatter plot for residuals (Dependent variable: Patient's perceived benefits score)

Results for the Logistic Regression Models for Patients' Willingness to Participate in Placebo-Controlled Clinical Trials:

Results in this section are described based on the different hypothetical scenarios presented in the questionnaire.

Results for Scenario 1: Allocation ratio of 1:1 for study drug to placebo plus standard of care:

The full multiple logistic regression model was statistically significant to predict a patient's willingness to participate in this scenario ($p > 0.01$). The model included intervention type, clinic type, patient's perceived severity and susceptibility scores, patient's knowledge score, patient's perceived benefits and barriers scores, and other patient's characteristics such as education and income as possible predictors. The model showed that the predictors explained 50.5% of the variability of the dependent variable. A patient's perceived barriers and perceived benefits scores were significant predictors ($p=0.02$, $p=0.04$, respectively). This means for each 1-point increase in a patient's perceived barriers score, there was a 2.27 increase in the odds for the patient to participate in this scenario. Similarly, for each 1-point increase in a patient's perceived benefits score, there was a 2.51 increase in the odds for the patient to participate in this scenario. Another significant predictor was previous participation in a clinical trial with an odds ratio of 6.71 ($p= 0.04$).

Furthermore, an interesting predictor was a patient's educational level. Patients with higher educational level had higher odds to participate in this scenario. The odds ratio for a patient with a high school degree increased from 26.9 ($p=0.11$) to 106.7 ($p=0.03$) for patients with a graduate degree compared to patients with less

than a high school degree (reference group). Another interesting predictor was clinic type. Although it was not a significant predictor but patients from the diabetes and nephrology clinics had odds ratios of 1.99 and 3.93, respectively, compared to the patients from the oncology clinic -reference group- (p=0.43, p= 0.12 respectively). Lastly, among the educational interventions, only patients in the video group had a higher odds ratio of 1.27 compared to the control group (p=0.81). Table 27 shows all the predictors in the model and their impact on a patient's willingness to participate in scenario 1.

Table 27. Predictors for patients' willingness to participate in scenario 1

Variable	B Coefficient	OR	95% C.I Upper -Lower		P Value
Clinic: Oncology (Ref.)	---	1	---	---	---
Diabetes	.689	1.991	.360	11.011	.430
Kidney	1.370	3.934	.698	22.160	.120
Intervention: Control (Ref.)	---	1	---	---	---
Booklet	-.092	.912	.147	5.668	.922
Video	.243	1.274	.167	9.702	.815
Booklet and Video	-.343	.710	.090	5.586	.745
Perceived severity score	.238	1.269	.675	2.385	.459
Perceived susceptibility score	-.530	.588	.313	1.104	.099
Knowledge	.090	1.095	.499	2.402	.822
Perceived barriers score	**.823**	**2.277**	**1.086**	**4.774**	**.029**
Perceived benefits score	**.921**	**2.512**	**1.013**	**6.231**	**.047**
Gender: Female (Ref.)	---	1	---	---	---
Male	.795	2.214	.624	7.859	.219
Age	**.079**	**1.082**	**1.014**	**1.156**	**.018**
Race: Non-Hispanic White (Ref.)	---	1	---	---	---
Hispanic	-.476	.621	.112	3.448	.586
African American	-2.691	.068	.002	1.857	.111
Other	-1.383	.251	.038	1.676	.154
Education: Less than high school (Ref.)	---	1	---	---	---
High School	3.296	26.993	.441	1653.913	.117
College	4.187	65.805	.975	4443.342	.051
Graduate degree	**4.671**	**106.783**	**1.364**	**8357.521**	**.036**
Income: < 10,000	---	1	---	---	---
10,000 - < 25,000	-1.495	.224	.027	1.848	.165
25,000 - < 40,000	.303	1.353	.155	11.815	.784
40,000 - < 55,000	-.101	.904	.026	31.072	.955
> 55,000	-1.690	.185	.011	3.003	.235
Previous participation in clinical trial: No (Ref.)	---	1	---	---	---
Yes	**1.904**	**6.712**	**1.032**	**43.665**	**.046**

Results for Scenario 1: Allocation ratio of 2:1 for study drug to placebo plus standard of care design:

The full multiple regression model for this scenario was not significant (p =0.49). There were, however, some predictors that increased patients' odds ratio to participate in this scenario. Patients' perceived benefits was a significant predictor with an odds ratio of 2.36 (p=0.01). Similar to the previous scenario, the higher the patient's educational level the higher the odds. The odds ratio for patients with high school degree increased form 1.47 (p=0.78) to 3.44 (p=.44) for patients with graduate degree compared to patients with less than high school degree. Moreover, patients from the diabetes clinic had an odds ratio of 1.37 compared to patients from the cancer clinic (p=0.68). Patients in the video group and patients in the booklet and video group had odds ratios of 1.19 (p=0.84) and 1.47 (p=0.67) –respectively- compared to the control group. Table 28 shows all the predictors in the model and their impact on patients' willingness to participate in the given scenario.

Table 28. Predictors for patients' willingness to participate in scenario 2

Variable	B Coefficient	OR	95% C.I Upper -Lower		P Value
Clinic: Oncology (Ref.)	---	1	---	---	---
Diabetes	.321	1.379	.294	6.464	.683
Kidney	.001	1.001	.260	3.850	.999
Intervention: Control (Ref.)	---	1	---	---	---
Booklet	-.142	.867	.158	4.755	.870
Video	.180	1.197	.197	7.276	.845
Booklet and Video	.388	1.474	.238	9.125	.676
Perceived severity score	-.192	.825	.481	1.413	.484
Perceived susceptibility score	.041	1.042	.614	1.767	.880
Knowledge	.129	1.138	.594	2.180	.697
Perceived barriers score	.176	1.192	.633	2.244	.586
Perceived benefits score	**.861**	**2.365**	**1.196**	**4.679**	**.013**
Gender: Female (Ref.)	---	1	---	---	---
Male	.459	1.583	.504	4.976	.432
Age	.032	1.033	.983	1.085	.201
Race: Non-Hispanic White (Ref.)	---	1	---	---	---
Hispanic	-.727	.483	.113	2.070	.327
African American	-.254	.776	.059	10.173	.847
Other	-.647	.524	.101	2.703	.440
Education: Less than high school (Ref.)	---	1	---	---	---
High School	.387	1.472	.092	23.679	.785
College	1.075	2.930	.158	54.225	.470
Graduate degree	1.237	3.445	.149	79.383	.440
Income: < 10,000	---	1	---	---	---
10,000 - < 25,000	-.505	.604	.124	2.937	.532
25,000 - < 40,000	.622	1.863	.280	12.403	.520
40,000 - < 55,000	-.938	.391	.023	6.772	.519
> 55,000	.370	1.448	.121	17.326	.770
Previous participation in clinical trial: No (Ref.)	---	1	---	---	---
Yes	.099	1.104	.292	4.179	.884

Results for Scenario 1: Allocation ratio of 3:1 for study drug to placebo plus standard of care design:

The full multiple regression model for this scenario was not significant (p =0.29). Patients' perceived benefits continued to be a significant predictor with an odds ratio of 2.48 (p=0.01). Similar to the previous scenario, the higher the patient's educational level the higher the odds. The odds ratio for patients a college degree was 1.41 and patients with graduate degree had an odds ratio of 6.75 compared to patients with less than high school degree (p=0.81, p=0.25 respectively). Moreover, patients in the video group had odds ratio of 2.24 compared to the control group (p=0.46). Lastly, patients with previous participation in a clinical study had an odds ratio of 1.40 (p=0.63). Table 29 shows all the predictors in the model and their impact on patients' willingness to participate in the given scenario.

Table 29. Predictors for Patients' willingness to participate in scenario 3

Variable	B Coefficient	OR	95% C.I Upper -Lower		P Value
Clinic: Oncology (Ref.)	---	1	---	---	---
Diabetes	-.313	.732	.154	3.471	.694
Kidney	-.303	.739	.175	3.112	.680
Intervention: Control (Ref.)	---	1	---	---	---
Booklet	-.758	.468	.073	3.022	.425
Video	.749	2.114	.289	15.457	.461
Booklet and Video	.009	1.009	.151	6.755	.993
Perceived severity score	-.175	.839	.464	1.519	.562
Perceived susceptibility score	-.099	.906	.529	1.549	.717
Knowledge	.234	1.264	.604	2.644	.534
Perceived barriers score	.128	1.137	.594	2.176	.699
Perceived benefits score	**.910**	**2.484**	**1.179**	**5.235**	**.017**
Gender: Female (Ref.)	---	1	---	---	---
Male	.426	1.532	.476	4.928	.474
Age	.015	1.015	.966	1.066	.552
Race: Non-Hispanic White (Ref.)	---	1	---	---	---
Hispanic	-.842	.431	.088	2.114	.299
African American	-.500	.607	.048	7.605	.699
Other	-.963	.382	.067	2.170	.277
Education: Less than high school (Ref.)	---	1	---	---	---
High School	-.151	.860	.050	14.866	.917
College	.349	1.417	.072	28.023	.819
Graduate degree	1.910	6.753	.247	184.625	.258
Income: < 10,000	---	1	---	---	---
10,000 - < 25,000	.401	1.494	.302	7.398	.623
25,000 - < 40,000	1.350	3.856	.571	26.028	.166
40,000 - < 55,000	-.635	.530	.029	9.568	.667
> 55,000	-1.120	.326	.023	4.709	.411
Previous participation in clinical trial: No (Ref.)	---	1	---	---	---
Yes	.340	1.405	.346	5.705	.634

Results for Scenario 4: Allocation ratio of 1:1 and placebo alone design:

Under this scenario, the full regression model was not significant (p=0.30). The model showed that patients in the video group and patients in the booklet and video had almost double the odds to participate in this scenario compared to patients in the control group (OR's = 1.99, p=0.40 and 1.80, p=0.47), respectively. In contrary to the previous three scenarios, the higher the patient's educational level the lower the odds. For instance, patients with high school degree or graduate degree had odds ratios of 0.21(p=0.24) and 0.17 (p=0.23) -respectively- compared to patients with less than high school. Also, patients from the diabetes clinic had an odds ratio of 0.26 compared to patients from the cancer clinic which was a significant predictor (p=0.04). Lastly, patients with previous participation in a clinical study had an odds ratio of 2.48 (p=0.10). Table 30 shows all the predictors in the model and their impact on patients' willingness to participate in the given scenario.

Table 30. Predictors for Patients' willingness to participate in scenario 4

Variable	B Coefficient	OR	95% C.I Upper -Lower		P Value
Clinic: Oncology (Ref.)	---	1	---	---	---
Diabetes	**-1.346**	**.260**	**.068**	**.991**	**.048**
Kidney	-.232	.793	.244	2.580	.700
Intervention: Control (Ref.)	---	1	---	---	---
Booklet	-.063	.939	.197	4.471	.937
Video	.689	1.991	.395	10.041	.404
Booklet and Video	.588	1.801	.365	8.885	.470
Perceived severity score	.248	1.282	.813	2.020	.285
Perceived susceptibility score	-.267	.766	.496	1.183	.229
Knowledge	.094	1.099	.607	1.987	.756
Perceived barriers score	-.056	.946	.542	1.651	.844
Perceived benefits score	-.075	.928	.505	1.704	.809
Gender: Female (Ref.)	---	1	---	---	---
Male	.032	1.032	.392	2.715	.949
Age	.030	1.030	.986	1.077	.184
Race: Non-Hispanic White (Ref.)	---	1	---	---	---
Hispanic	.561	1.752	.512	5.997	.372
African American	-2.481	.084	.005	1.392	.084
Other	-.202	.817	.215	3.104	.767
Education: Less than high school (Ref.)	---	1	---	---	---
High School	-1.533	.216	.016	2.899	.247
College	-1.361	.257	.018	3.722	.319
Graduate degree	-1.774	.170	.009	3.176	.235
Income: < 10,000	---	1	---	---	---
10,000 - < 25,000	.132	1.142	.291	4.478	.849
25,000 - < 40,000	**1.721**	**5.592**	**1.094**	**28.590**	**.039**
40,000 - < 55,000	2.243	9.420	.448	198.135	.149
> 55,000	-.175	.839	.110	6.398	.866
Previous participation in clinical trial: No (Ref.)	---	1	---	---	---
Yes	.910	2.484	.830	7.429	.104

Results for Scenario 5: Allocation ratio of 2:1 and placebo alone design:

The full regression model was not significant for this scenario (p=0.74). Similar to the last scenario, patients in the booklet and video had higher odds to participate in this scenario compared to patients in the control group (OR= 1.65, p=0.51). Like the previous scenario, the higher the patient's educational level the lower the odds to participate in this scenario. Patients with high school degree or graduate degree had odds ratios of 0.16 (p=0.16) and 0.0.17(p=0.22) –respectively- compared to patients with less than high school. Also, patients from the diabetes clinic had an odds ratio of 0.40 (p=0.14) compared to patients from the cancer clinic. Lastly, previous participation in a clinical study had an odds ratio of 1.91 (p=0.21). Table 31 shows all the predictors in the model and their impact on patients' willingness to participate in the given scenario.

Table 31. Predictors for Patients' willingness to participate in scenario 5

Variable	B Coefficient	OR	95% C.I Upper -Lower		P Value
Clinic: Oncology (Ref.)	---	1	---	---	---
Diabetes	-.906	.404	.118	1.378	.148
Kidney	-.311	.733	.231	2.322	.597
Intervention: Control (Ref.)	---	1	---	---	---
Booklet	-.349	.705	.159	3.120	.645
Video	.103	1.109	.238	5.173	.896
Booklet and Video	.502	1.652	.360	7.578	.519
Perceived severity score	.049	1.050	.682	1.617	.825
Perceived susceptibility score	-.067	.936	.620	1.412	.751
Knowledge	.201	1.223	.686	2.178	.495
Perceived barriers score	-.235	.791	.459	1.361	.397
Perceived benefits score	.025	1.025	.568	1.850	.934
Gender: Female (Ref.)	---	1	---	---	---
Male	-.086	.917	.360	2.338	.857
Age	.019	1.019	.978	1.062	.364
Race: Non-Hispanic White (Ref.)	---	1	---	---	---
Hispanic	.275	1.316	.418	4.140	.639
African American	-2.358	.095	.006	1.450	.090
Other	-.239	.787	.215	2.881	.718
Education: Less than high school (Ref.)	---	1	---	---	---
High School	-1.811	.164	.013	2.061	.161
College	-1.411	.244	.018	3.267	.286
Graduate degree	-1.758	.172	.010	2.953	.225
Income: < 10,000	---	1	---	---	---
10,000 - < 25,000	.002	1.002	.268	3.741	.997
25,000 - < 40,000	1.166	3.209	.694	14.833	.135
40,000 - < 55,000	2.037	7.669	.372	158.032	.187
> 55,000	.044	1.045	.151	7.212	.964
Previous participation in clinical trial: No (Ref.)	---	1	---	---	---
Yes	.652	1.919	.689	5.344	.212

Results for Scenario 6: Allocation ratio of 3:1 and placebo alone design:

Under this scenario, the full regression model was not significant (p=0.53). The model showed that patients in the video group and patients in the booklet and video group continued to have higher odds ratios for this scenario compared to the control group (OR's= 1.67, p=0.53 and 1.99, p=0.38, respectively). Similar to the previous scenario, patients with higher educational levels had lower odds ratios to participate in this scenario. For instance, patients with high school degree or graduate degree had odds ratios of 0.13 (p=0.12) and 0.17 (p=0.22) –respectively- compared to patients with less than high school. Also, patients from the diabetes clinic had an odds ratio of 0.46 (p=0.23) compared to patients from the cancer clinic. Lastly, patients with previous participation in a clinical study had an odds ratio of 2.04 (p=0.18). Table 32 shows all the predictors in the model and their impact on patients' willingness to participate in the given scenario.

Table 32. Predictors for Patients' willingness to participate in scenario 6

Variable	B Coefficient	OR	95% C.I Upper -Lower		P Value
Clinic: Oncology (Ref.)	---	1	---	---	---
Diabetes	-.775	.461	.129	1.646	.233
Kidney	.019	1.019	.314	3.307	.975
Intervention: Control (Ref.)	---	1	---	---	---
Booklet	-.362	.697	.154	3.141	.638
Video	.515	1.673	.335	8.364	.531
Booklet and Video	.691	1.996	.415	9.601	.389
Perceived severity score	.153	1.165	.748	1.815	.498
Perceived susceptibility score	-.198	.820	.536	1.255	.360
Knowledge	.150	1.162	.651	2.073	.612
Perceived barriers score	-.190	.827	.475	1.442	.503
Perceived benefits score	-.151	.860	.466	1.587	.629
Gender: Female (Ref.)	---	1	---	---	---
Male	-.375	.687	.260	1.817	.449
Age	.020	1.021	.979	1.065	.340
Race: Non-Hispanic White (Ref.)	---	1	---	---	---
Hispanic	-.089	.915	.283	2.956	.882
African American	-2.129	.119	.009	1.657	.113
Other	-.140	.869	.233	3.248	.835
Education: Less than high school (Ref.)	---	1	---	---	---
High School	-1.981	.138	.011	1.713	.123
College	-1.700	.183	.014	2.431	.198
Graduate degree	-1.731	.177	.011	2.961	.228
Income: < 10,000	---	1	---	---	---
10,000 - < 25,000	.518	1.679	.417	6.756	.466
25,000 - < 40,000	**2.196**	**8.990**	**1.728**	**46.782**	**.009**
40,000 - < 55,000	1.614	5.024	.360	70.092	.230
> 55,000	.283	1.327	.181	9.718	.780
Previous participation in clinical trial: No (Ref.)	---	1	---	---	---
Yes	.715	2.045	.716	5.842	.182

Results for the Multiple Linear Regression Models for Patients' Willingness to Participate in Placebo Controlled Clinical Trials:

This section includes the results for the multiple linear regression models to predict the impact of the different independent variables on the likelihood score for patients to participate in placebo-controlled clinical trials. The results are described based on the different hypothetical scenarios presented in the questionnaire.

Results for Scenario 1: Allocation ratio of 1:1 for study drug to placebo plus standard of care design

The full multiple linear regression model was statistically significant to predict patients' willingness to participate in scenario 1 ($p < 0.01$). The model included intervention type, clinic type, patient's perceived severity and susceptibility scores, patient's knowledge score, patient's perceived benefits and barriers scores, and other patient's characteristics such as education and income as possible predictors. The model showed that the predictors explained 42.8% of the variability of the dependent variable. Patients' perceived barriers and patients' perceived benefits were significant predictors ($p=0.02$ and $p=0.01$, respectively). This means for each 1-point increase in a patient's perceived barriers score, there was 0.39-unit increase in the likelihood score for the patient to participate in the given scenario (when all other independent variables are held constant). Similarly, for each 1-point increase in a patient's perceived benefits score, there was 0.34-unit increase in the likelihood score for the patient to participate in the given scenario (when all other independent variables are held constant).

Another significant predictor was patients' educational level. The coefficient score increased from 1.54 (p=0.05) for patients with a high school degree to 2.10 (p=0.01) for patients with a graduate degree compared to patients with less than high school degree – the reference group- (when all other independent variables are held constant).

As far as the educational interventions, patients in the video group had a coefficient of 0.56 point compared to the control group (p=0.26). Patients randomized to the booklet and video group had a coefficient of 0.28 point compared to the control group (p=0.56).

Another interesting predictor was previous participation in clinical trials. Patients with previous participation had a coefficient of 0.51 point for the likelihood score compared to patients with no previous participation (p=0.12). Table 33 shows all the predictors in the model and their impact on patients' willingness to participate in the given scenario.

Table 33. Predictors for patients' willingness score to participate in scenario 1

Variable	B Coefficient	P Value	VIF*
Clinic: Oncology (Ref.)	---	---	---
Diabetes	.637	.101	1.830
Kidney	.596	.117	1.761
Intervention: Control (Ref.)	---	---	---
Booklet	.100	.836	2.451
Video	.568	.268	2.723
Booklet and Video	.289	.565	2.621
Knowledge	-.091	.612	2.261
Perceived severity score	.236	.107	1.684
Perceived susceptibility score	-.217	.116	2.080
Perceived barriers score	**.398**	**.022**	1.737
Perceived benefits score	**.488**	**.012**	1.413
Gender: Female (Ref.)	---	---	---
Male	-.064	.835	1.324
Age	.017	.203	1.351
Race: Non-Hispanic White (Ref.)	---	---	---
Hispanic	-.259	.485	1.799
African American	-.876	.200	1.563
Other	-.435	.314	1.622
Education: Less than high school (Ref.)	---	---	---
High School	**1.548**	**.050**	7.923
College	**1.651**	**.043**	8.471
Graduate degree	**2.107**	**.019**	7.270
Income: < 10,000	---	---	---
10,000 - < 25,000	-.242	.573	2.370
25,000 - < 40,000	.484	.326	1.948
40,000 - < 55,000	-.131	.867	1.810
> 55,000	-.576	.368	2.867
Previous participation in clinical trial: No (Ref.)	---	---	---
Yes	.525	.121	1.262

* Variance Inflation Factor

Results for Scenario 2: Allocation ratio of 2:1 for Study drug to placebo plus standard of care design

The full model for this scenario was statistically significant ($p < 0.01$). The model explained 37% of the variability of the dependent variable. In this model, a patient's perceived benefits was a significant predictor with a coefficient of 0.55 point ($p < 0.01$). Similar to the previous scenario, the coefficient score increased from 1.32 (p=0.09) for patients with a high school degree to 1.83 (p=0.03) for patients with a graduate degree compared to patients with less than high school degree.

Moreover, patients in the video group had a coefficient of 0.67 point compared to patients in the control group (p=0.18). Patients in the booklet and video group, had a coefficient of 0.55 point compared to patients in the control group. This indicates that the video intervention continued to have the highest coefficient on patients' likelihood score for this scenario compared to the other groups.

Furthermore, patients with previous participation in clinical trials had a coefficient of 0.38 point for the likelihood score compared to patients with no previous participation (p=0.25). Table 34 shows all the predictors in the model and their impact on patients' willingness to participate in the given scenario.

Table 34. Predictors for patients' willingness score to participate in scenario 2

Variable	B Coefficient	P Value	VIF*
Clinic: Oncology (Ref.)	---	---	---
Diabetes	.410	.283	1.830
Kidney	.301	.421	1.761
Intervention: Control (Ref.)	---	---	---
Booklet	.157	.743	2.451
Video	.671	.186	2.723
Booklet and Video	.557	.263	2.621
Knowledge	-.060	.737	2.261
Perceived severity score	.142	.326	1.684
Perceived susceptibility score	-.138	.312	2.080
Perceived barriers score	.239	.161	1.737
Perceived benefits score	**.554**	**< 0.01**	1.413
Gender: Female (Ref.)	---	---	---
Male	.087	.776	1.324
Age	.011	.393	1.351
Race: Non-Hispanic White (Ref.)	---	---	---
Hispanic	-.433	.239	1.799
African American	-.911	.178	1.563
Other	-.338	.429	1.622
Education: Less than high school (Ref.)	---	---	---
High School	1.320	.090	7.923
College	1.322	.101	8.471
Graduate degree	**1.834**	**.038**	7.270
Income: < 10,000	---	---	---
10,000 - < 25,000	-.152	.721	2.370
25,000 - < 40,000	.489	.316	1.948
40,000 - < 55,000	-.149	.848	1.810
> 55,000	-.572	.366	2.867
Previous participation in clinical trial: No (Ref.)	---	---	---
Yes	.384	.250	1.262

* Variance Inflation Factor

Results for Scenario 3: Allocation ratio of 3:1 for study drug to placebo plus standard of care design

The full model for this scenario was statistically significant ($p < 0.01$). The model explained 35.1% of the variability of the dependent variable. A patient's perceived benefits score was a significant predictor with a coefficient of 0.45 point (p=0.01). A patient's perceived barriers score was almost significant with a coefficient of 0.30 point (p=0.07).

Similar to the previous scenario, the higher the patient education the higher the coefficient. The coefficient score increased from 1.33 (p=0.08) for patients with a high school degree to 1.80 (p=0.04) for patients with a graduate degree compared to patients with less than high school degree.

Moreover, like the previous two scenarios, patients in the video group had the highest coefficient on patients' likelihood score for this given scenario compared to the other groups. The coefficient for patients in the video group was 0.50 point compared to patients in the control group. Patients in the booklet and video group had a coefficient of 0.34 point compared to patients in the control group.

Lastly, patients with previous participation in a clinical trials had a coefficient of 0.44 point for the likelihood score compared to patients with no previous participation in clinical studies. Table 35 shows all the predictors in the model and their impact on patients' willingness to participate in the given scenario.

Table 35. Predictors for patients' willingness score to participate in scenario 3

Variable	B Coefficient	P Value	VIF*
Clinic: Oncology (Ref.)	---	---	---
Diabetes	.137	.721	1.830
Kidney	.098	.794	1.761
Intervention: Control (Ref.)	---	---	---
Booklet	.151	.754	2.451
Video	.508	.319	2.723
Booklet and Video	.341	.495	2.621
Knowledge	-.070	.695	2.261
Perceived severity score	.157	.279	1.684
Perceived susceptibility score	-.192	.163	2.080
Perceived barriers score	.303	.078	1.737
Perceived benefits score	**.459**	**.018**	1.413
Gender: Female (Ref.)	---	---	---
Male	.126	.682	1.324
Age	.010	.427	1.351
Race: Non-Hispanic White (Ref.)	---	---	---
Hispanic	-.307	.406	1.799
African American	-.963	.158	1.563
Other	-.264	.539	1.622
Education: Less than high school (Ref.)	---	---	---
High School	1.339	.088	7.923
College	1.408	.083	8.471
Graduate degree	**1.809**	**.042**	7.270
Income: < 10,000	---	---	---
10,000 - < 25,000	-.036	.932	2.370
25,000 - < 40,000	.451	.358	1.948
40,000 - < 55,000	.153	.845	1.810
> 55,000	-.364	.567	2.867
Previous participation in clinical trial: No (Ref.)	---	---	---
Yes	.448	.183	1.262

* Variance Inflation Factor

Results for Scenario 4: Allocation ratio of 1:1 for study drug to placebo alone:

The full model for this scenario was not statistically significant with no significant predictors (p =.30). Unlike the previous scenarios, Patients' perceived barriers and patients' perceived benefits scores were not significant predictors. Also, patient educational level did not have the same trend like the previous three scenarios. Patients with a graduate degree had a coefficient of 0.07 point while patients with a college degree had a coefficient of 0.50 compared to patients with less than a high school degree.

Moreover, unlike the previous scenarios, patients in the booklet and video group had the highest coefficient on patients' likelihood score for this given scenario compared to the other groups. The coefficient for patients in the booklet and video group was 1.09 point compared to patients in the control group (p=0.11). While patients in the video group had a coefficient of 0.77 unit compared to patients in the control group (p=0.27).

Lastly, previous participation in clinical trials continued to have the same trend of the previous three scenarios. Patients with previous participation in clinical trials had a positive coefficient of 0.66 point but yet, it was not significant (p=0.16). Table 36 shows all the predictors in the model and their impact on patients' willingness to participate in the given scenario.

Table 36. Predictors for patients' willingness score to participate in scenario 4

Variable	B Coefficient	P Value	VIF*
Clinic: Oncology (Ref.)	---	---	---
Diabetes	-.566	.294	1.830
Kidney	.447	.397	1.761
Intervention: Control (Ref.)	---	---	---
Booklet	.309	.648	2.451
Video	.777	.277	2.723
Booklet and Video	1.097	.119	2.621
Knowledge	-.182	.469	2.261
Perceived severity score	.324	.113	1.684
Perceived susceptibility score	-.231	.229	2.080
Perceived barriers score	-.125	.600	1.737
Perceived benefits score	.113	.674	1.413
Gender: Female (Ref.)	---	---	---
Male	.365	.397	1.324
Age	.013	.488	1.351
Race: Non-Hispanic White (Ref.)	---	---	---
Hispanic	.075	.884	1.799
African American	-1.803	.060	1.563
Other	-.114	.849	1.622
Education: Less than high school (Ref.)	---	---	---
High School	.221	.840	7.923
College	.505	.655	8.471
Graduate degree	.075	.952	7.270
Income: < 10,000	---	---	---
10,000 - < 25,000	-.300	.617	2.370
25,000 - < 40,000	.905	.189	1.948
40,000 - < 55,000	.798	.468	1.810
> 55,000	-.830	.353	2.867
Previous participation in clinical trial: No (Ref.)	---	---	---
Yes	.660	.162	1.262

* Variance Inflation Factor

Results for Scenario 5: Allocation ratio of 2:1 for study drug to placebo alone:

The full model for this scenario was not statistically significant (p=.36). Patients' perceived barriers and patients' perceived benefits continued to be not significant predictors. Moreover, patients in the booklet and video group continued to have the highest coefficient on patients' likelihood score for this given scenario compared to the other groups. The coefficient for patients in the booklet and video group was 1.15 points compared to patients in the control group (p=0.11). While patients in the video group had a coefficient of 0.77 point compared to patients in the control group (p=0.30).

Lastly, patients with previous participation continued to have a positive coefficient of 0.70 point but yet, it was not significant. Table 37 shows all the predictors in the model and their impact on patients' willingness to participate in the given scenario.

Table 37. Predictors for patients' willingness score to participate in scenario 5

Variable	B Coefficient	P Value	VIF*
Clinic: Oncology (Ref.)	---	---	---
Diabetes	-.606	.281	1.830
Kidney	.441	.423	1.761
Intervention: Control (Ref.)	---	---	---
Booklet	.198	.779	2.451
Video	.773	.300	2.723
Booklet and Video	1.157	.115	2.621
Knowledge	-.145	.581	2.261
Perceived severity score	.294	.167	1.684
Perceived susceptibility score	-.182	.364	2.080
Perceived barriers score	-.175	.483	1.737
Perceived benefits score	.147	.598	1.413
Gender: Female (Ref.)	---	---	---
Male	.399	.376	1.324
Age	.012	.511	1.351
Race: Non-Hispanic White (Ref.)	---	---	---
Hispanic	.096	.859	1.799
African American	**-1.991**	**.047**	1.563
Other	-.192	.759	1.622
Education: Less than high school (Ref.)	---	---	---
High School	.074	.948	7.923
College	.413	.725	8.471
Graduate degree	.108	.933	7.270
Income: < 10,000	---	---	---
10,000 - < 25,000	-.371	.553	2.370
25,000 - < 40,000	.828	.249	1.948
40,000 - < 55,000	.862	.452	1.810
> 55,000	-.941	.313	2.867
Previous participation in clinical trial: No (Ref.)	---	---	---
Yes	.700	.155	1.262

* Variance Inflation Factor

Results for Scenario 6: Allocation ratio of 3:1 for study drug to placebo alone:

The full model for this scenario was not statistically significant with no significant predictors (p =.34). Patients in the booklet and the video group, however, continued to have the highest coefficient on patients' likelihood score for this given scenario compared to the other groups. The coefficient for patients in the booklet and the video group was 1.10 point compared to control group (p=value= 0.13). While patients in the video group had a coefficient of 0.76 compared to patients in the control group (p=0.30).

Previous participation continued to have a positive coefficient of 0.68 but yet, it was not significant (p=0.16). Table 38 shows all the predictors in the model and their impact on patients' willingness to participate in the given scenario.

Table 38. Predictors for patients' willingness score to participate in scenario 6

Variable	B Coefficient	P Value	VIF*
Clinic: Oncology (Ref.)	---	---	---
Diabetes	-.468	.405	1.830
Kidney	.492	.371	1.761
Intervention: Control (Ref.)	---	---	---
Booklet	.094	.894	2.451
Video	.762	.307	2.723
Booklet and Video	1.101	.134	2.621
Knowledge	-.122	.640	2.261
Perceived severity score	.270	.204	1.684
Perceived susceptibility score	-.220	.272	2.080
Perceived barriers score	-.134	.592	1.737
Perceived benefits score	.061	.826	1.413
Gender: Female (Ref.)	---	---	---
Male	.384	.394	1.324
Age	.013	.495	1.351
Race: Non-Hispanic White (Ref.)	---	---	---
Hispanic	-.078	.885	1.799
African American	**-2.126**	**.034**	1.563
Other	-.133	.832	1.622
Education: Less than high school (Ref.)	---	---	---
High School	.181	.874	7.923
College	.359	.760	8.471
Graduate degree	.158	.902	7.270
Income: < 10,000	---	---	---
10,000 - < 25,000	-.276	.659	2.370
25,000 - < 40,000	1.050	.145	1.948
40,000 - < 55,000	1.087	.344	1.810
> 55,000	-.911	.329	2.867
Previous participation in clinical trial: No (Ref.)	---	---	---
Yes	.686	.164	1.262

* Variance Inflation Factor

Results According to Clinic Type:

1. The Oncology Clinic:

Patients' Demographics:

Thirty-six patients from the oncology clinic participated in this study. There were 9 participants in each study group. The average age for this clinic was 54.17 years (±11.99). The majority of the study participants identified themselves as Non-Hispanic White (n=17, 47.2%). Previous participation in a clinical trial was reported by 9 patients (25%). Over all, there was no significant differences in patients' characteristics among the study groups. Table 39 depicts all patients' characteristics from the oncology clinic among the study groups.

Table 39. Baseline characteristics for study participants from the oncology clinic: n(%)

Patient characteristic / study group	The Booklet n=9	The video n=9	The booklet and video n=9	The control n=9	P value
Age (mean ± SD)	54.00 (9.70)	51.78 (9.49)	56.63 (12.62)	54.11 (16.01)	0.86
Gender					
Male	4 (44.4)	5 (55.6)	4 (44.4)	5 (55.6)	0.93
Female	5 (55.6)	4 (44.4)	5 (55.6)	4 (44.4)	
Race					
Non-Hispanic White	4 (44.4)	6 (66.7)	4 (44.4)	3 (33.3)	
Hispanic	3 (33.3)	1 (11.1)	2 (22.2)	2 (22.2)	
African American	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	0.62
Other	1 (11.1)	1 (11.1)	3 (33.3)	4 (44.4)	
Education					
Less than high school	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	
High school	1 (11.1)	4 (44.4)	2 (22.2)	2 (22.2)	0.30
College	2 (22.2)	3 (33.3)	5 (55.6)	4 (44.4)	
Graduate	6 (66.7)	2 (22.2)	2 (22.2)	2 (22.2)	
Marital status					
Single	0 (0.0)	4 (44.4)	2 (22.2)	2 (22.2)	
Married	7 (77.8)	5 (55.6)	7 (77.8)	7 (77.8)	0.10
Divorce	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Widowed	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	
Income					
< $10,000	1 (11.1)	2 (22.2)	1 (11.1)	2 (22.2)	
$ 10,000 - ≤ $ 25,000	1 (11.1)	2 (22.2)	1 (11.1)	4 (44.4)	
$ 25,000 - ≤ $ 40,000	2 (22.2)	1 (11.1)	3 (33.3)	2 (22.2)	0.59
$ 40,000 - ≤ $ 55,000	2 (22.2)	0 (0.0)	1 (11.1)	1 (11.1)	
> $ 55,000	3 (33.3)	4 (44.4)	3 (33.3)	0 (0.0)	
Previous Participant in a clinical study					
Yes	2	2	2	3	
No	7	7	7	6	0.93

Patients' Perceived Threats:

1. Patient's Perceived Susceptibility:

Patients in the video group and patients in the booklet and video group had the lowest perceived susceptibility score of 0.33 (±1.32 and ±1.67 respectively). Patients in the control group had a score of 0.38 (±1.57). Patients in the booklet group had the highest score of 0.66 (±1.80). There was no significant difference among the different group related to patients' perceived susceptibility score (p= 0.96).

2. Patient's Perceived Severity:

Patients in the booklet and video group had the highest perceived severity score of 1.88 (±0.72) followed by patients in the booklet group with a score of 1.85 (±0.95). Patients in the video group had a score of 1.70 (±1.26) while patients in the control group had the lowest score of 1.11 (±1.47). There was no significant difference among the different groups related to patients' perceived severity score (p= 0.45).

Patients' Knowledge Score:

Patients in the video group and patients in the booklet and video group had the highest knowledge score of 9.67 out of 10 possible points (±0.50). Patients in the booklet group had a knowledge score of 9.44 points (±1.13). The score for the patients in the control group was the lowest with 8.33 points (±1.41). There was a statistical significant difference in the knowledge score among the groups ($p < 0.01$). In the multiple comparisons test, all the three interventional groups had a statistical significant difference in comparison to the control group. Among the three interventional groups, there was no significant difference in patients' knowledge

score. Table 40 shows the results for patients' knowledge score among the study groups.

Table 40. Patients' knowledge score according to study groups within the oncology clinic

Study Group	Mean	Std. Deviation	Minimum	Maximum	P Value
Control	8.33	1.41	5	10	
Booklet	9.44	1.13	7	10	
Video	9.67	.50	9	10	< **0.01**
Booklet and Video	9.67	.50	9	10	

Patients' perceptions related to placebo controlled clinical trials:

Results in this section range from -3 to +3 points. A higher score indicates a more positive perception with less barriers toward placebo-controlled clinical trials. Similarly, a higher score in a patient's perceived benefits indicates more expected benefits and a more positive perception towards placebo-controlled clinical trials.

Patients' Perceived Barriers:

Patients in the three interventional groups had higher scores in the perceived barriers compared to the control group. Patients in the video group had the highest score for the perceived barriers perception with an average score of 2.00 (±1.00). Patients in the booklet group had a score of 1.74 points (±0.99), followed by patients in the booklet and video group of 1.62 points (±0.78). The lowest average score for perceived barriers was in the control group with a score of 1.51 points (±0.85). There was no statistical significant difference among the four groups (p=0.71).

Table 41. Patients' perceived barriers score according to study groups within the oncology clinic

Study Group	Mean	Std. Deviation	Minimum	Maximum	P Value
Control	1.51	.85	.33	3.00	0.71
Booklet	1.74	.99	.33	3.00	
Video	2.00	1.00	.00	3.00	
Booklet and Video	1.62	.78	.67	3.00	

Patients' Perceived Benefits:

There was no statistical difference among the study groups related to patients' perceived benefits (p=0.29). Patients in the video group had the highest average score of 2.25 (±0.72). Patients in the booklet group had an average score of 2.00 (±0.68), followed by patients in the control group with an average score of 1.88 (±0.68). Lastly, patients in the booklet and video group had the lowest average score of 1.40 (±1.17).

Table 42. Patients' perceived benefits score according to study groups within the oncology clinic

Study Group	Mean	Std. Deviation	Minimum	Maximum	P Value
Control	1.88	.68	.67	3.00	0.20
Booklet	2.00	.68	1.00	3.00	
Video	2.25	.72	1.00	3.00	
Booklet and Video	1.40	1.17	-1.33	2.67	

Patients' Willingness to Participate in Placebo-Controlled Clinical Trials:

Results for Scenario 1: Allocation ratio of 1:1 for study drug to placebo plus standard of care design:

Seven (77.8 %) patients in the booklet group and 7 (77.8 %) patients in the video group said Yes to participate in this scenario. In the booklet and video group, 5 (55.6%) patient said Yes compared to 4 (44.4%) in the control group. There was no statistical difference among the four groups related to the number of patients who were willing to participate in the given study scenario (p=0.35).

Table 43. Number of patients willing to participate in scenario 1 within the oncology clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	4	5	0.35
Booklet	7	2	
Video	7	2	
Booklet and Video	5	4	
Total	23	13	

Results for Scenario 2: Allocation ratio of 2:1 for study drug to placebo plus standard of care design:

Eight (88.9 %) patients in the video group and 7 (55.6%) in the booklet group said Yes to participate in this scenario. The booklet and video group, and the control group had 6 (66.7%) patients each who accepted the given scenario. There was no statistical difference among the four groups related to the number of patients who were willing to participate in the given study scenario (p=0.65).

Table 44. Number of Patients willing to participate in scenario 2 within the oncology clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	6	3	0.65
Booklet	7	2	
Video	8	1	
Booklet and Video	6	3	
Total	27	9	

Results for Scenario 3: Allocation ratio of 3:1 for study drug to placebo plus standard of care design:

In the video group, 8 (88.9 %) patients said Yes to participate in this scenario. Each of the booklet group, and the control group had 7 (77.8%) patients who accepted the given scenario. In the booklet and video group, there were 6 (66.7%) patients accepted to participate in this scenario. There was no statistical difference among the four groups related to the number of patients who were willing to participate in the given study scenario (p=0.73).

Table 45. Number of patients willing to participate in scenario 3 within the oncology clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	7	2	0.73
Booklet	7	2	
Video	8	1	
Booklet and Video	6	3	
Total	28	8	

Results for Scenario 4: Allocation ratio of 1:1 for study drug to placebo alone design:

Each of the booklet group and the booklet and video group had 5 (55.6 %) patients accepted to participate in this scenario. In the video group, there were 4 (44.4%) patients and 6 patients (66.7%) in the control group who said Yes to this scenario. There was no statistical difference among the four groups related to the number of patients who were willing to participate in the given study scenario (p=0.82).

Table 46. Number of patients willing to participate in scenario 4 within the oncology clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	6	3	0.82
Booklet	5	4	
Video	4	5	
Booklet and Video	5	4	
Total	20	16	

Results for Scenario 5: Allocation ratio of 2:1 for study drug to placebo alone design:

Six patients (55.6%) in the booklet group and 5 (55.6%) patients in the booklet and video group accepted to participate in the given study scenario. In the video group, 4 (44.4%) patients and 6 patients (66.7%) in the control group said Yes to this scenario. There was no statistical difference among the four groups related to the

number of patients who were willing to participate in the given study scenario (p=0.82).

Table 47. Number of patients willing to participate in scenario 5 within the oncology clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	6	3	0.82
Booklet	5	4	
Video	4	5	
Booklet and Video	5	4	
Total	20	16	

Results for Scenario 6: Allocation ratio of 3:1 for study drug to placebo alone design:

Both the booklet group and the video group had 4 (44.4 %) patients accepted to participate in the given study scenario. In the booklet and video group, there were 6 (66.7%) patients accepted the given scenario while the control group had 5 patients (55.6%) said Yes to this scenario. There was no statistical difference between the four groups related to the number of patients who were willing to participate in the given study scenario (p=0.74).

Table 48. Number of patients willing to participate in scenario 6 within the oncology clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	5	4	0.74
Booklet	4	5	
Video	4	5	
Booklet and Video	6	3	
Total	19	17	

2. Results for the Diabetes Clinic:

Patients' Demographics:

Thirty-six patients from the diabetes clinic participated in this study. There were 9 participants in each study group. The average age for this clinic was 58.0 years (±7.96). The majority of the study participants identified themselves as Hispanic (n=19, 52.8%). Previous participation in a clinical trial was reported by 11 patients (30.6%). Over all, there was no significant difference in patients' characteristics among the study groups. Table 49 depicts all patients' characteristics from the diabetes clinic among the study groups.

Table 49. Baseline characteristics for study participants from the diabetes clinic: n(%)

Patient characteristic / study group	The Booklet n=9	The video n=9	The booklet and video n=9	The control n=9	P value
Age (mean ± SD)	60.67 (7.48)	57.44 (6.89)	57.11 (9.03)	56.78 (9.03)	0.72
Gender					
Male	5 (55.6)	5 (55.6)	5 (55.6)	5 (55.6)	0.82
Female	4 (44.4)	4 (44.4)	4 (44.4)	4 (44.4)	
Race					
Non-Hispanic White	3 (33.3)	2 (22.2)	2 (22.2)	4 (44.4)	
Hispanic	3 (33.3)	6 (66.7)	6 (66.7)	4 (44.4)	
African American	2 (22.2)	1 (11.1)	0 (0.0)	0 (0.0)	0.62
Other	1 (11.1)	0 (0.0)	1 (11.1)	1 (11.1)	
Education					
Less than high school	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	
High school	3 (33.3)	2 (22.2)	3 (33.3)	3 (33.3)	0.81
College	3 (33.3)	5 (55.6)	3 (33.3)	5 (55.6)	
Graduate	3 (33.3)	2 (22.2)	2 (22.2)	1 (11.1)	
Marital status					
Single	1 (11.1)	4 (44.4)	4 (44.4)	5 (55.6)	
Married	4 (44.4)	3 (33.3)	3 (33.3)	3 (33.3)	0.55
Divorce	4 (44.4)	2 (22.2)	2 (22.2)	1 (11.1)	
Widowed	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Income					
< $10,000	2 (22.2)	2 (22.2)	5 (55.6)	2 (22.2)	
$ 10,000 - ≤ $ 25,000	4 (44.4)	4 (44.4)	2 (22.2)	2 (22.2)	
$ 25,000 - ≤ $ 40,000	3 (33.3)	2 (22.2)	0 (0.0)	4 (44.4)	0.37
$ 40,000 - ≤ $ 55,000	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
> $ 55,000	0 (0.0)	1 (11.1)	2 (22.2)	1 (11.1)	
Previous Participant in a clinical study					
Yes	3	3	2	3	
No	6	6	7	6	0.94

Patients' Perceived Threats:

1. Patients' Perceived Susceptibility:

Patients in the control group had a perceived susceptibility score of 1.55 (±1.23). Patients in the booklet had a score of 1.16 (±1.50) while patients in the video group had a score of 1.55 (±1.13). Patients in the booklet and video group had the lowest score of 0.50 (±1.56) while patients in the video group had a score of 0.81 (±1.44). There was no significant difference among the different group related to patients' perceived susceptibility score (p= 0.32).

2.Patients' Perceived Severity:

Patients in the control group had the highest perceived severity score of 2.59 (±0.32). Patients in the video group had the lowest perceived severity score of 1.40 (±1.28). Patients in the booklet group had a score of 1.70 (±1.08) while patients in the booklet and video group had a score of 1.59 (±1.15). There was no significant difference among the different group related to patients' perceived severity score (p= 0.09).

Patients' Knowledge Score:

Patients in the booklet and video group had the highest knowledge score of 9.67 out of 10 possible points (±0.70). Patients in the video group had a knowledge score of 9.56 points (±0.72) followed by patients in the booklet group with a score of 9.44 (±0.52). The score for the patients in the control group was the lowest of 8.11 points (±1.05). There was a statistical significant difference in the knowledge score among the groups ($p < 0.01$). In the multiple comparisons test, all the three interventional groups had a significant statistical difference in comparison to the

control group. Among the three interventional groups, there was no statistical significant difference in patients' knowledge score. Table 50 shows the results for patients' knowledge score among the study groups.

Table 50. Patients' knowledge score according to study groups within the diabetes clinic

Study Group	Mean	Std. Deviation	Minimum	Maximum	P Value
Control	8.11	1.05	7	10	
Booklet	9.44	.52	9	10	
Video	9.56	.72	8	10	**< 0.01**
Booklet and Video	9.67	.70	8	10	

Patients' Perceptions related to placebo controlled clinical trials:

Results in this section range from -3 to +3 points. A higher score indicates a more positive perception with less barriers toward placebo-controlled clinical trials. Similarly, a higher score in a patient's perceived benefits indicates more expected benefits and a more positive perception towards placebo-controlled clinical trials.

1. Patients' Perceived Barriers:

Patients in the three interventional groups had higher scores in the perceived barriers compared to the control group. Patients in the video group had the highest score for the perceived barriers perception with an average score of 2.00 (±0.86). Patients in the booklet and video group had a score of 1.96 points (±0.71), followed by patients in the booklet group of 1.51 points (±1.41). The lowest average score for perceived barriers was in the control group with a score of 0.88 points (±1.15). There was no significant statistical difference among the four groups (p=0.12).

Table 51. Patients' perceived barriers score according to study groups within the diabetes clinic.

Study Group	Mean	Std. Deviation	Minimum	Maximum	P Value
Control	.88	1.15	-.33	3.00	0.12
Booklet	1.51	1.41	-1.33	3.00	
Video	2.00	.86	.67	3.00	
Booklet and Video	1.96	.71	1.00	3.00	

2. Patients' Perceived Benefits:

There was no statistical difference among the study groups related to patients' perceived benefits (p=0.29). Patients in the booklet and video group had the highest average score of 2.18 out of 3 possible points (±0.68). Patients in the video group had an average score of 2.14 (±0.50), followed by patients in the booklet group with an average score of 2.00 (±0.66). Lastly, patients in the control group had the lowest average score of 1.96 (±0.53).

Table 52. Patients' perceived benefits score according to study groups within the diabetes clinic.

Study Group	Mean	Std. Deviation	Minimum	Maximum	P Value
Control	1.96	.53	1.00	2.67	0.83
Booklet	2.00	.66	1.00	3.00	
Video	2.14	.50	1.67	3.00	
Booklet and Video	2.18	.68	1.00	3.00	

Patients' Willingness to Participate in Placebo-Controlled Clinical Trials:

Results for Scenario 1: Allocation ratio of 1:1 for study drug to placebo plus standard of care design:

The booklet group and the booklet and video group had 7 (77.8 %) patients each who accepted to participate in this scenario. There were 6 (66.7%) patients in the video group and 8 (88.9%) patients in the control group who accepted this scenario. There was no statistical difference among the four groups related to this scenario (p=0.73).

Table 53. Number of patients willing to participate in scenario 1 within the diabetes clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	8	1	0.73
Booklet	7	2	
Video	6	3	
Booklet and Video	7	2	
Total	28	8	

Results for Scenario 2: Allocation ratio of 2:1 for study drug to placebo plus standard of care design:

The booklet group and the booklet and video group had 8 (88.9 %) patients each accepted to participate in the given study scenario. There were 7 (77.8%) patients in the video group and 7 (77.8%) patients in the control group who accepted this scenario. There was no statistical difference among the four groups related to this scenario (p=0.84).

Table 54. Number of patients willing to participate in scenario 2 within the diabetes clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	7	2	0.84
Booklet	8	1	
Video	7	2	
Booklet and Video	8	1	
Total	30	6	

Results for Scenario 3: Allocation ratio of 3:1 for study drug to placebo plus standard of care design:

There were 7 patients (77.8 %) in the video group as well as in the booklet and video who accepted to participate in this scenario. In the booklet group, there were 8 (88.9%) patients said Yes to this scenario compared to 6 (66.7%) in the control group. There was no statistical difference among the four groups related to the number of patients who were willing to participate in this scenario (p=0.73).

Table 55. Number of patients willing to participate in scenario 3 within the diabetes clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	6	3	0.73
Booklet	8	1	
Video	7	2	
Booklet and Video	7	2	
Total	28	8	

Results for Scenario 4: Allocation ratio of 1:1 for study drug to placebo alone:

The booklet group had 1 patient (11.1 %) who said Yes to participate in this scenario. In the video group, there were 3 (33.3%) patients who said Yes compared to 4 (44.4%) in the booklet and video group. There were 3 (33.3%) patients in the control group accepted this given scenario. There was no statistical difference among the four groups related to the number of patients who were willing to participate in this scenario (p=0.47).

Table 56. Number of patients willing to participate in scenario 4 within the diabetes clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	3	6	0.47
Booklet	1	8	
Video	3	6	
Booklet and Video	4	5	
Total	11	25	

Results for Scenario 5: Allocation ratio of 2:1 for study drug to placebo alone:

The booklet group had 1 patient (11.1 %) who said Yes to participate in this scenario. In the video group, there were 3 patients (33.3%) patients who said Yes compared to 5 (55.6%) in the booklet and video group. There were 4 (44.4%) patients in the control group who accepted the given scenario. There was no statistical difference among the four groups related to the number of patients who were willing to participate in this scenario (p=0.23).

Table 57. Number of patients willing to participate in scenario 5 within the diabetes clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	4	5	0.23
Booklet	1	8	
Video	3	6	
Booklet and Video	5	4	
Total	13	23	

Results for Scenario 6: Allocation ratio of 3:1 for study drug to placebo alone:

The booklet group had 1 patient (11.1 %) who said Yes to participate in this scenario. In the video group, there were 3 (33.3%) patients who accepted this scenario compared to 4 (44.4%) patients in the booklet and video group. There were 4 (44.4%) patients in the control group who accepted this scenario. There was no statistical difference among the four groups related to the number of patients who were willing to participate in this scenario (p=0.39).

Table 58. Number of patients willing to participate in scenario 6 within the diabetes clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	4	5	0.39
Booklet	1	8	
Video	3	6	
Booklet and Video	4	5	
Total	12	24	

3. Results for the Nephrology Clinic:

Thirty sixty patients from the nephrology clinic participated in this study. There were 9 participants in each study group. The average age for this clinic was 56.81 years (±15.23). The oldest group was the control with an average age of 62.33 (±17.88) and the youngest was the video group with an age of 48.89 (±13.95). The majority of the study participants identified themselves as Hispanic (n=14, 38.9%). Previous participation in a clinical trial was reported by 10 patients (27.8%). Over all, there was no significant difference among in patients' characteristics among the study groups. Table 59 depicts all patients' characteristics from the nephrology clinic among the study groups.

Table 59. Baseline characteristics for study participants from the nephrology clinic: n(%)

Patient characteristic / study group	The Booklet n=9	The video n=9	The booklet and video n=9	The control n=9	P value
Age (mean ± SD)	57.33 (14.94)	48.89 (13.95)	58.67 (12.95)	62.33 (17.88)	0.29
Gender					
Male	5 (55.6)	4 (44.4)	4 (44.4)	4 (44.4)	0.93
Female	4 (44.4)	5 (55.6)	5 (55.6)	5 (55.6)	
Race					
Non-Hispanic White	5 (55.6)	1 (11.1)	2 (22.2)	3 (33.3)	
Hispanic	3 (33.3)	5 (55.6)	2 (22.2)	4 (44.4)	
African American	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	0.25
Other	1 (11.1)	2 (22.2)	5 (55.6)	1 (11.1)	
Education					
Less than high school	1 (11.1)	1 (11.1)	0 (0.0)	1 (11.1)	
High school	5 (55.6)	4 (44.4)	5 (55.6)	6 (66.7)	0.97
College	2 (22.2)	3 (33.3)	3 (33.3)	2 (22.2)	
Graduate	1 (11.1)	1 (11.1)	1 (11.1)	0 (0.0)	
Marital status					
Single	3 (33.3)	2 (22.2)	3 (33.3)	4 (44.4)	
Married	3 (33.3)	4 (44.4)	3 (33.3)	1 (11.1)	0.79
Divorce	3 (33.3)	2 (22.2)	2 (22.2)	4 (44.4)	
Widowed	0 (0.0)	1 (11.1)	1 (11.1)	0 (0.0)	
Income					
< $10,000	2 (22.2)	3 (33.3)	1 (11.1)	5 (55.6)	
$ 10,000 - ≤ $ 25,000	5 (55.6)	4 (44.4)	7 (77.8)	3 (33.3)	
$ 25,000 - ≤ $ 40,000	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0.52
$ 40,000 - ≤ $ 55,000	0 (0.0)	1 (11.1)	0 (0.0)	1 (11.1)	
> $ 55,000	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	
Previous Participant in a clinical study					
Yes	3	3	1	3	
No	6	6	8	6	0.64

Patients' Perceived Threats:

1.Patients' Perceived Susceptibility:

Patients in the control group and patients in the booklet had the highest perceived susceptibility score of 0.83 (±1.22 and ±1.11 respectively). Patients in the booklet and video had a score of 0.72 (±1.06) while patients in the video group had a score of 0.55 (±1.66). There was no significant difference among the different group related to patients' perceived susceptibility score (p= 0.96).

2. Patients' Perceived Severity:

Patients in the control group and patients in the booklet and video group had the highest perceived severity score of 1.29 (±1.12 and ±1.45 respectively). Patients in the booklet group and patients in the video group had a perceived severity score of 0.92 (±1.01 and ±1.63 respectively). There was no significant difference among the different group related to patients' perceived severity score (p= 0.87).

Patients' Knowledge Score:

Patients in the booklet had the highest knowledge score of 9.89 out of 10 possible points (±0.33). Patients in the video group had a knowledge score of 9.78 points (±0.44) followed by patients in the booklet and video group with a score of 9.67 (±0.70). The score for the patients in the control group was the lowest of 7.67 points (±1.73). There was a significant statistical difference in the knowledge score among the groups ($p < 0.01$). In the multiple comparisons test, all the three interventional groups had a statistical significant difference in comparison to the control group. Among the three interventional groups, there was no statistical

significant difference in patients' knowledge score. Table 60 shows the results for patients' knowledge score among the study groups.

Table 60. Patients' knowledge score according to study groups within the nephrology clinic

Study Group	Mean	Std. Deviation	Minimum	Maximum	P Value
Control	7.67	1.73	4	10	< **0.01**
Booklet	9.89	.33	9	10	
Video	9.78	.44	9	10	
Booklet and Video	9.67	.70	8	10	

Patients' Perceptions related to placebo controlled clinical trials:

Results in this section range from -3 to +3 points. A higher score indicates a more positive perception and less barriers towards placebo-controlled clinical trials. Similarly, a higher score in a patient's perceived benefits indicates more expected benefits and a more positive perception towards placebo-controlled clinical trials.

1. Patients' Perceived Barriers:

Patients in the three interventional groups had higher scores in the perceived barriers compared to the control group. Patients in the booklet and video group had the highest score for the perceived barriers perception with an average score of 2.25 points (±0.46). Patients in the booklet group had a score of 1.96 points (±0.63), followed by patients in the video group of 1.92 points (±0.89). The lowest average score for perceived barriers was in the control group with a score of 0.22 points (±1.01). There was a statistical significant difference among the four groups ($p < 0.01$).

Table 61. Patients' perceived barriers score according to study groups within the nephrology clinic

Study Group	Mean	Std. Deviation	Minimum	Maximum	P Value
Control	.22	1.01	-1.00	2.33	< **0.01**
Booklet	1.96	.63	1.33	3.00	
Video	1.92	.89	.00	3.00	
Booklet and Video	2.25	.46	1.67	3.00	

2. Patients' Perceived Benefits:

There was no statistical difference among the study groups related to patients' perceived benefits (p=0.41). Patients in the booklet group had the highest average score of 2.00 out of 3 possible points (±.91). Patients in the video group had an average score of 1.88 (±0.94), followed by patients in the booklet and video group with an average score of 1.70 (±1.21). Lastly, patients in the control group had the lowest average score of 1.48 (±0.98).

Table 62. Patients' perceived benefits score according to study groups within the nephrology clinic

Study Group	Mean	Std. Deviation	Minimum	Maximum	P Value
Control	1.48	.98	.00	3.00	0.72
Booklet	2.00	.91	.66	3.00	
Video	1.88	.94	.66	3.00	
Booklet and Video	1.70	1.21	-1.33	3.00	

Patients' Willingness to Participate in Placebo-controlled Clinical Trials:

Results for Scenario 1: Allocation ratio of 1:1 for study drug to placebo plus standard of care design:

The video group and the booklet and video group had 7 (77.8 %) patients each said Yes to participate in the given study scenario. There were 6 (66.7%) patients in the booklet group followed by 5 (44.4%) patients in the control group accepted this scenario. There was no statistical difference among the four groups related to this scenario (p=0.69).

Table 63. Number of patients willing to participate in scenario 1 within the nephrology clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	5	4	0.69
Booklet	6	3	
Video	7	2	
Booklet and Video	7	2	
Total	25	11	

Results for Scenario 2: Allocation ratio of 2:1 for study drug to placebo plus standard of care design:

The booklet and video group had 7 (77.8 %) patients accepted to participate in the given study scenario. There were 6 (66.7%) patients in the video group as well as in the booklet group who accepted this scenario. The control group had 5 (55.6%) patients accepted this scenario. There was no statistical difference among the four groups related to this scenario (p=0.80).

Table 64. Number of patients willing to participate in scenario 2 within the nephrology clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	5	4	0.80
Booklet	6	3	
Video	6	3	
Booklet and Video	7	2	
Total	24	12	

Results for Scenario 3: Allocation ratio of 3:1 for study drug to placebo plus standard of care design:

The video group had 8 (88.9%) patients who accepted to participate in this scenario. There were 7 (77.8 %) patients in the booklet and video group and 5 (55.6%) patients in the control group who accepted this scenario. There was no statistical difference among the four groups related to this scenario (p=0.31).

Table 65. Number of patients willing to participate in scenario 3 within the nephrology clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	5	4	0.31
Booklet	5	4	
Video	8	1	
Booklet and Video	7	2	
Total	25	11	

Results for Scenario 4: Allocation ratio of 1:1 for study drug to placebo alone:

The video group and the booklet and video group had 5 (55.6 %) patients each accepted to participate in this study scenario. There were 4 (44.4%) patients in the booklet group and 3 (33.3%) patients in the control group who accepted this scenario. There was no statistical difference among the four groups related to this scenario (p=0.74).

Table 66. Number of patients willing to participate in scenario 4 within the nephrology clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	3	6	0.74
Booklet	4	5	
Video	5	4	
Booklet and Video	5	4	
Total	17	19	

Results for Scenario 5: Allocation ratio of 2:1 for study drug to placebo alone:

The booklet and video group had 5 (55.6 %) patients who said Yes to participate in this scenario. There were 4 (44.4%) patients in the booklet group and 4 (44.4%) patients in the video group who accepted this scenario. The control group had 3 (33.3%) patients who were willing to participate in this scenario. There was no statistical difference among the four groups related to this scenario (p=0.82).

Table 67. Number of patients willing to participate in scenario 5 within the nephrology clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	3	6	0.82
Booklet	4	5	
Video	4	5	
Booklet and Video	5	4	
Total	16	20	

Results for Scenario 6: Allocation ratio of 3:1 for study drug to placebo alone:

The booklet and video group had 5 (55.6 %) patients who said Yes to participate in this scenario. There were 4 (44.4%) patients in the booklet group and 4 (44.4%) patients in the video group who accepted this scenario. The control group had 3 (33.3%) patients who were willing to participate in this scenario. There was no statistical difference among the four groups related to this scenario (p=0.82).

Table 68. Number of patients willing to participate in scenario 6 within the nephrology clinic

Study Group	Number of Accepters	Number of Decliners	P Value
Control	3	6	0.82
Booklet	4	5	
Video	4	4	
Booklet and Video	5	4	
Total	16	20	

Patients' Reasons for Accepting or Declining the Participation in Placebo-Controlled Clinical Trials:

Fifty-six patients answered the optional open ended question regarding reasons to participate in placebo-controlled clinical trials. The first listed reason was personal benefit (n=38/56, 67.85%). The second reason was benefiting others (n=32/56, 57.14%). Table 82 lists all the reasons reported by the patients who were included in this study for accepting the participation in placebo-controlled clinical trials. In contrast, 42 patients answered the question related to reasons for declining the participation in placebo-controlled clinical trials. The first reason reported was side effects (n=11/42, 26.19%). Six patient said because they are very sick and 5 patients reported that my medication works well. Four patients reported that the reason for not participating was because of placebos. Table 69 lists all the reasons reported by the patients who were included in the study for declining the participation in placebo-controlled clinical trials.

Table 69. Reasons reported by patients for accepting or declining participation in placebo-controlled clinical trials.

Reasons for accepting	**Number (%) N=56**
- Personal benefits	38 (67.85)
- Benefiting others	32 (57.14)
- Altruism	6 (10.71)
- Controlled by an ethical committee	2 (3.57)
- Curious	2 (3.57)
- Trust my doctor	1 (1.78)
- Monetary	1 (1.78)
Reasons for declining	**Number (%) N=42**
- Side effects	11 (26.19)
- Very sick	6 (14.28)
- My treatment works well	5 (11.90)
- Short time	4 (9.52)
- Ask my doctor	3 (7.14)
- Don't want to take placebo	4 (9.52)
- Bad timing	1 (2.38)
- Not interested	1 (2.38)
- I don't want to	1 (2.38)
- I don't feel comfortable	1 (2.38)

Results for the Cognitive Load of the Educational Interventions:

The booklet and the video had a median score of 0.00 (Neither high nor low mental effort) for the mental effort question. The booklet had a median score of 1.00 (Easy) and the video had a median score of 2.00 (very easy) for the difficulty questions. The minimum score for the booklet and the video for the difficulty question was 0.00 which means that none of the patients assessed either the booklet or the video as difficult. Table 70 shows the results for the cognitive load questions.

Table 70. The cognitive load responses for the educational materials.

Study group/ Cognitive load question	The booklet	The video	The booklet and video
1- In reading/ watching the educational material, I used: (+3 Extremely low mental effort to -3 Extremely high mental effort).	Minimum: -3 Maximum: 3 Mean: 0.33 Median: 0.00	Minimum: -3 Maximum: +3 Mean: 0.04 Median:0.00	Minimum: -3 Maximum:3 Mean: 0.43 Median:1.0
2- How easy or difficult was this educational material to understand? (+3: Extremely easy to -3 Extremely difficult).	Minimum: 0 Maximum: 3 Mean: 1.59 Median: 1.00	Minimum: 0 Maximum: 3 Mean: 1.74 Median: 2.00	Minimum: 0 Maximum: 3 Mean: 1.44 Median:1.00

The Validity and Reliability of the Questionnaire:

The reliability and validity of certain questions of the questionnaire had been assessed in previous studies.[10,72,73,74,75] Table 71 shows all the questions from the previous studies that were used in the finalized questionnaire. In spite of that, another assessment was conducted to assess the validity and reliability of the finalized questionnaire. The questionnaire was pilot tested on 5 patients to establish face validity. During the face validity phase, the questionnaire was tested to assure

readability, comprehension of instructions, and clarity. Based upon feedback from patients, minor modifications were made to the questionnaire to eliminate any ambiguous phrasing. The questionnaire reliability was assessed using Cronbach's alpha, a measure of internal consistency. Cronbach's alpha was measured for all the five different scales of the questionnaire; perceived threats, patients' perceptions, patient' knowledge, patients' willingness to participate in scenarios 1, 2 and 3 and patients' willingness to participate in scenarios 4, 5 and 6 scale. Cronbach's alpha coefficients ranged from 0.52 to 0.99. The reliability of the finalized questionnaire is satisfactory as 3 scales out of 5 had acceptable values.[76,77] Table 72 shows the results for the reliability test for the finalized questionnaire.

Table 71. The questions that were included in the finalized questionnaire from previous studies.

Scale and Questions	Previous Studies
Perceived severity:	
1- My diabetes is serious	- Yan (2009)[75]
2- I face more life difficulties because of my diabetes.	- Yan (2009)[75]
3- My family faces more life difficulties because of my diabetes.	- Yan (2009)[75]
Perceived susceptibility:	
1- I worry that my diabetes will get worse.	- Yan (2009)[75]
Patients' Knowledge:	
1- Randomization means that my treatment will be chosen by chance.	- Campbell et al. (2008)[10]
2- The Institutional Review Board meets before a study begins to make sure that the rights and welfare of patients are protected	- Campbell et al. (2008)[10]
3- The Data Monitoring Board is responsible for stopping a clinical study if the study drug works better and more effective than the placebo.	- Campbell et al. (2008)[10]
4- You must not talk to others (family member or a friend) about the clinical study before making your decision whether or not to participate .	- Campbell et al. (2008)[10]
Patients' perceptions (Perceived barriers and benefits):	
1- I am suspicious of placebo clinical trials.	- Banda et al. (2012)[72]
2- Placebo clinical trials are not ethical.	- Banda et al. (2012)[72]
3- I am confident the group of people who approve placebo clinical trials make sure all participants are treated fairly.	- Banda et al. (2012)[72]
4- There may be benefits for me if I participate in a placebo clinical trial.	- Banda et al. (2012)[72]
5- I will still get the best medical care even if I participated in placebo clinical studies.	- Banda et al. (2012)[72]
6- There may be benefits for other people like me if I participate in a placebo clinical trial.	- Banda et al. (2012)[72]

Table 72. The results for the reliability test for the finalized questionnaire.

Scale	Number of items	Cronbach's alpha
Perceived threats (severity and susceptibility)	5	0.74
Patients' perceptions (Perceived barriers and benefits)	6	0.67
Patients' knowledge score	10	0.52
Patients' willingness to participate (Scenario 1,2 and3)	3	0.97
Patients' willingness to participate (Scenario 4,5 and6)	3	0.99

Summary:

The results showed that the educational interventions were able to significantly increase patient knowledge about placebo-controlled clinical trials compared to the control group. Patients in the video group and patients in the booklet and video group had the highest knowledge score of 9.66 (±0.55 and ±0.62, respectively) followed by patients in the booklet group with a knowledge score of 9.59 (±0.74). There was a significant statistical difference in the knowledge score among the four groups ($p < 0.01$).

The educational interventions significantly increased patient perceived barriers score ($p < 0.01$), reflecting lower perceived barriers, compared to the control group. The booklet intervention and the video intervention increased patient perceived benefits score compared to the control group. Although there was no statistical significant difference among the groups, the educational interventions increased the number of patients in each hypothetical scenario. Patient knowledge was not a significant predictor of patients' perceived barriers, benefits, or their willingness to participate in clinical trials.

Table 73. Summary for the study hypotheses and their main results.

Hypothesis	Results
Hypothesis 1: There is no difference in a patient's knowledge related to placebo-controlled clinical trials among the educational booklet intervention, video intervention, both interventions (the booklet plus the video) and the standard consent form group.	- There was a significant difference in patients' knowledge score among the groups, with higher knowledge scores for all 3 interventions, compared to the control group. - Significant predictors for patients' knowledge score were: - Educational interventions. - Income (Patients with an annual income of between $10,000 and $25,000 and patients with an annual income of between $40,000 and $55,000 compared to patients with an annual income of less than $10,000).
Hypothesis 2: There is no difference on a patient's perceptions (perceived barriers and perceived benefits) related placebo-controlled clinical trials among the educational booklet, the video, both interventions (the booklet plus the video) and the standard consent form group.	- There was a significant statistical difference in patients' perceived barriers score among the four groups, with higher barriers scores (less barriers) for all 3 interventions, compared to the control group. - Significant predictor for patients' perceived barriers score was: - Educational interventions. - There was no statistical difference in patients' perceived benefits score among the four groups. - Significant predictor for patients' perceived benefits score was: - Previous participation in clinical trials compared to naive patients.

Table 73 (continued). Summary for the study hypotheses and their main results.

Hypothesis	Results
Hypothesis 3: There is no difference on a patient's willingness to participate in placebo controlled clinical trials among the educational booklet, the video, both interventions (the booklet plus the video) and the standard consent form group.	- There was no statistical difference in patients' willingness to participate in placebo-controlled clinical trials among the four groups. - Significant predictors for patients' willingness to participate in placebo-controlled clinical trials were: For scenario 1: - Perceived barriers score (higher scores predicted higher odds of willingness). - Perceived benefits score (higher scores predicted higher odds of willingness). - Age (older age predicted higher odds of willingness). - Education (graduate school patients had higher odds of willingness compared to less than high school patients). and previous participation in clinical trials. For scenario 2: Perceived benefits score higher scores predicted higher odds of willingness). For scenario 3: Perceived benefits score higher scores predicted higher odds of willingness). For scenario 4: - Clinic type (diabetic patients had higher odds of willingness compared to patient from the oncology clinic). - Income (patients with an annual income of between $25,000 and $40,000 had higher odds of willingness compared to patients with an annual income of less than $10,000). For scenario 5: No significant predictors. For scenario 6: Income (patients with an annual income of between $25,000 and $40,000 had higher odds of willingness compared to patients with an annual income of less than $10,000).

CHAPTER 5

DISCUSSION

Introduction:

This study aimed to design educational interventions to improve patient knowledge of placebo controlled clinical trials. The study also measured the impact of educational interventions on patient perceptions (perceived benefits and perceived barriers) related to placebo-controlled clinical trials. Lastly, the study measured the impact of educational interventions on patient willingness to participate in placebo controlled clinical trials. The discussion section presents a comprehensive analysis of results, implications, limitations, and future directions.

Patients Demographics:

The average age for the overall study sample was 56.32 years (±12.03). According to the CDC, over 85% of cancer diagnoses from 2005 through 2009 in New Mexico were over the age of 50 years.[78] Moreover, the mean age at diagnosis of diabetes among adults is 53.8 years.[79] For patients with chronic kidney disease, risk increases after the age of 50 years old.[80] The majority of the study participants identified themselves as Hispanic followed by Non-Hispanic whites (Table 13). Previous participation in a clinical trial was reported by 30 patients (27.8%) and seven patients had participated in a placebo controlled clinical trial. A similar number (28%) of previous participation in clinical trials was reported in a previous study by Sood and colleagues.[81] Overall, these numbers related to patients' characteristics included in this study showed that our sampling process was successful in representing the population of New Mexico state as well as the included diseases in this study.

Patient's Knowledge Score:

The results showed that the educational interventions were able to significantly increase patient knowledge about placebo-controlled clinical trials compared to the control group. The difference in the knowledge score between patients in the booklet group and the control group was 15.6% points. The difference in the knowledge score between patients in the video group and patients in the booklet and video group compared to the control group was 16.3% points. The highest knowledge score was for patients in the booklet group from the nephrology clinic with a score of 9.89 (±0.33) points and the lowest knowledge score was for the patients in the control group from the nephrology clinic with an average score of 7.67 (±1.73) points. The differences in patient knowledge score from this study are consistent with other studies in the literature that aimed to improve patients' knowledge regarding clinical trials.[15,16] For example, Aaronson and colleagues[15] reported a difference of 17.2% for the interventional group compared to the control group. Table 5 in chapter 2 shows studies that reported significant results had differences in patient knowledge ranged from 3.0% to 20.1% for the interventional groups compared to the control groups.

For patients' knowledge score per individual question, there was a significant difference between the interventional groups and the control group in six questions. These questions were number 1, 2, 4, 7, 8 and 9. These questions are related to important aspects of placebo-controlled clinical trials. These aspects include the placebo definition, receiving the same medical care for the study drug and placebo group, the role of a data monitoring board, using placebos in serious medical

conditions and patient right to discuss the participation decision in a clinical trial with family members or friends. Thus, the results of this study show the importance of educational materials for increasing patient knowledge and understanding of such essential elements of clinical trials.

The improvement in patients' knowledge regarding placebo-controlled clinical trials for the interventional groups was expected. Patients in the interventional groups read or watched the educational materials and therefore, learned more about placebo-controlled clinical trials in comparison to patients in the control group. The consent form used in this study had limited information related to placebo-controlled clinical trials. This consent form information was limited to the definition of a placebo, randomization and a patient's right to withdraw at any time (questions number 1, 3 and 10 in section 3 of the questionnaire). In spite of the availability of this information in the standard consent form for the control group there was a statistical difference between the control group and the interventional groups related to question 1 and 3 (Table 15, chapter 4). This indicates that regardless the availability of information in the consent form, the interventions were effective, therefore, it is important to consider the way information was presented. This finding signifies the importance of using CLT principles within the educational materials and their impact on decreasing patients' intrinsic load and optimizing their germane load.

Patients' Perceived Barriers:

The educational materials used in the three interventional groups significantly increased patients' perceived barriers score, reflecting lower perceived barriers,

towards placebo-controlled clinical trials. Patients in the video group had the highest mean score for perceived barriers (Table 16, chapter 4). Patient barriers related to participation in clinical trials can vary. Barriers could relate to the study drugs and their side effects, the study design and protocol, patient inconvenience or the relationship with their physicians.[22] Other barriers are related to patient attitude towards clinical trials.[13,22,44] These patient attitudinal barriers include perceptions of being treated as a guinea pig and distrust of the medical profession.[13,22,44] The educational materials used in the present study aimed to reduce these patient attitudinal barriers. The questionnaire measured patient perceived barriers related to the ethical aspect of using placebos in clinical trials, being suspicious of placebo-controlled clinical trials, and study approvals from ethics committees. The educational materials significantly reduced patients' perceptions of barriers related to placebo-controlled clinical trials, and as such, could potentially increase future participation in such trials.

Patients' Perceived Benefits:

Although there was no statistically significant difference among the study groups, the booklet intervention and the video intervention increased patient perceived benefits score compared to the control group. Patients in the video group had the highest average score (Table 17, chapter 4)

Patients in the booklet group and patients in the video group had higher perceived benefits scores compared to the control group, which was an expected outcome. Patients in the booklet and video group, however, scored slightly lower than the patients in the control group, which was an unexpected result (Table 17, chapter

4). Further examination was performed to investigate a possible explanation. There were two patients from the whole sample that had a negative perceived benefits score of 1.33. These two patients were randomized in the booklet and video group which resulted in lowering the average score for the group. Therefore, a further analysis was performed after excluding these two patients from the booklet and video group. The new perceived benefit average score for the group increased to 2.01, which is higher than the average score in the control group. The results from the new analysis showed that there is a consistency among all three interventional groups in terms of increasing patient perceived benefits compared to the control group. Table 74 shows the average perceived benefits scores for the study groups after the new analysis, although these differences were still not statistically significant.

Table 74. Patients' perceived benefits score after excluding the two patients with negative scores

Study Group	N	Mean	Standard Deviation
Control	27	1.77	±.76
Booklet	27	2.00	±.73
Video	27	2.09	±.73
Booklet and Video	25	2.01	±.60

Patient benefits were presented in the educational materials by explaining the indirect benefits from participation in placebo-controlled clinical trials. For example, participants in the placebo control group benefit from the attention that they receive

from the study investigators and staff. Also, the educational materials explained to patients that their participation may provide medical benefit to future patients. However, the educational materials did not demonstrate possible direct medical benefits to patients in the placebo arm from participation in placebo-controlled clinical trials. Some researchers have argued that potential direct medical benefits from placebos should be explained to patients.[82] They have argued that placebos are often described in consent forms as inert substances without any pharmacological activities.[82] Theses researchers presented data from a review study that examined participant information leaflets and found that only one of 45 leaflets mentioned that a placebo could have some medical benefits.[83] The researchers argued that it may be appropriate to consider the placebo effect as a benefit when the study outcome is subjective or modifiable by psychological factors, such as the outcomes of Parkinson's disease or pain relief.[82] They also suggested that potential placebo benefits should be included in the informed consent process for clinical trials with subjective outcomes.[82]

This argument regarding the medical benefits of using placebos has some validity and the medical community should consider inclusion of potential placebo benefits for trials with subjective outcomes. At the same time, and in order to prevent excessive inclusion of potential benefits in consent forms, possible side effects from placebos should also be included. A previous study that examined participant information leaflets found that only 4 of 45 leaflets mentioned possible side effects from placebos.[83] Therefore, it seems more ethical for future patients to be aware of possible benefits and side effects from using placebos.

Patient's Willingness to Participate in Placebo-controlled Clinical Trials:

The educational materials increased the number of patients who were willing to participate in the given hypothetical scenarios, although the differences were not statistically significant. The three interventional groups showed higher numbers of accepters compared to the control group for scenarios 1, 2 and 3 which specified the study drug plus standard of care or placebo plus standard of care with allocation ratios of 1:1, 2:1 and 3:1, respectively, for one year. However, for scenarios 4, 5 and 6 which specified the study drug alone or placebo alone with 3 different allocation ratios of 1:1, 2:1 and 3:1 respectively, for a one-month period, only the booklet plus the video group had higher numbers of accepters compared to the control group. Further examination of the data was performed to understand why only the booklet and the video had more number of accepters and not the other interventional groups.

After looking for all possible reasons, we found that the booklet plus video group was the only group that did not include African American patients. There were 3 African American patients in the booklet group, 3 in the video group and 1 in the control group. Out of these 7 African American patients, 6 rejected the participation in scenarios 4, 5 and 6. The lack of African American patients might help explain why the booklet plus video group had higher numbers of accepters compared to the other interventional groups in scenarios 4, 5 and 6. This finding might relate to a previous discussion about the issue of the representation of African Americans in clinical trials. African Americans are generally underrepresented in clinical trials.[84] There are different barriers attributed to the low representation of African Americans in clinical trials. Some barriers are related to individual-characteristics, such as age,

socioeconomic status, and comorbid condition.[84] Other barriers are related to historical reasons.[84] African Americans have expressed some suspicion and distrust of medical research and investigators as a result of the Tuskegee Study. Understanding these challenges by the medical community can aid in the development of different strategies and educational interventions to more effectively include African Americans into clinical trials.

The questionnaire of this study asked patients about the likelihood of their participating in a hypothetical placebo-controlled clinical trial using six different scenarios. The first three scenarios (scenarios 1, 2 and 3) used three different allocation ratios of 1:1, 2:1 and 3:1 for the study drug to placebo plus standard of care. This study hypothesized that increasing the chance to receive the study drug would lead patients to accept the scenario and therefore, increase the willingness of their participation. Unexpectedly, the study results did not show increasing trends in the number of accepters associating with the increase in the allocation ratio. The video group was the only group showing that trend for scenarios 1, 2 and 3 (Figures 20-27).

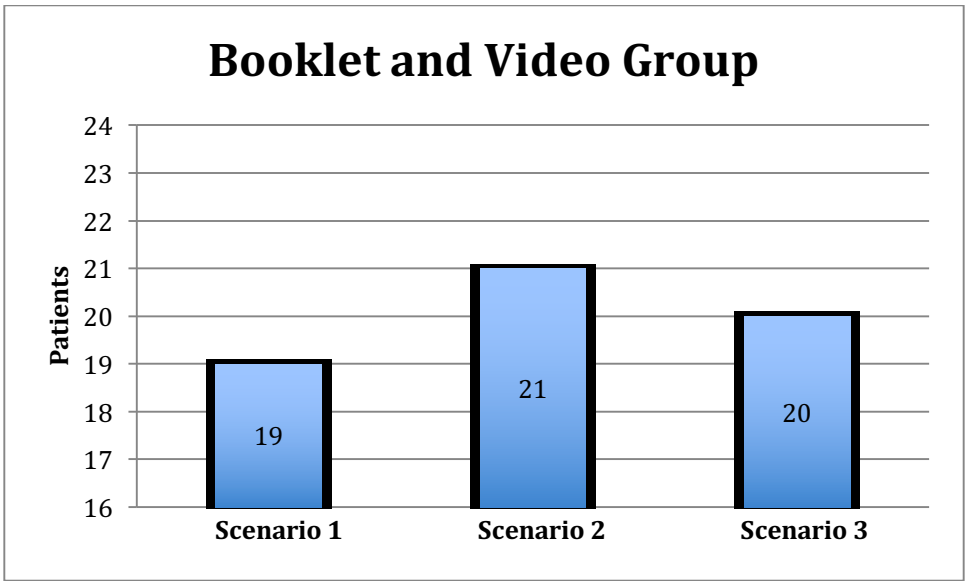


Figure 20: Number of accepters in scenarios 1-3 for the booklet and video group

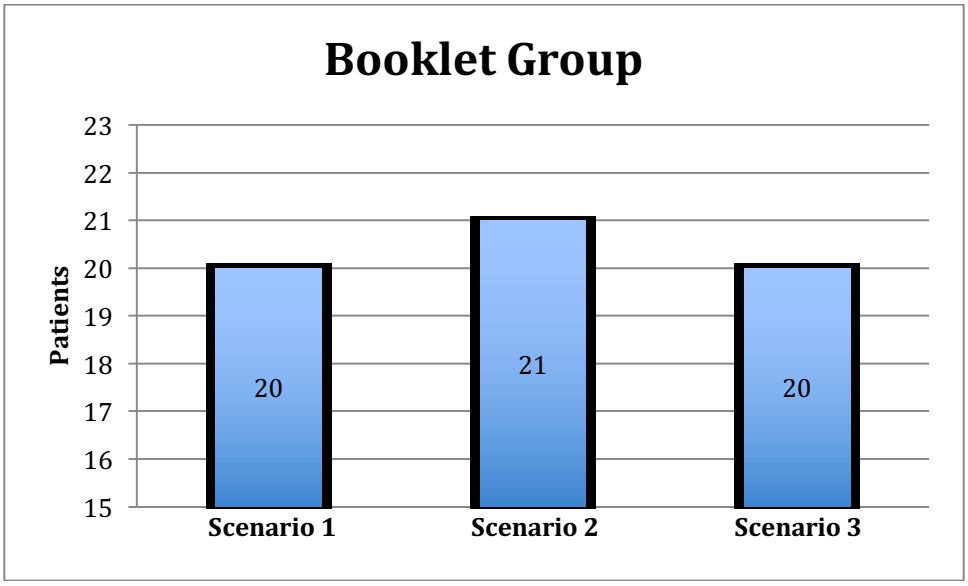


Figure 21: Number of accepters in scenarios 1-3 for the booklet group

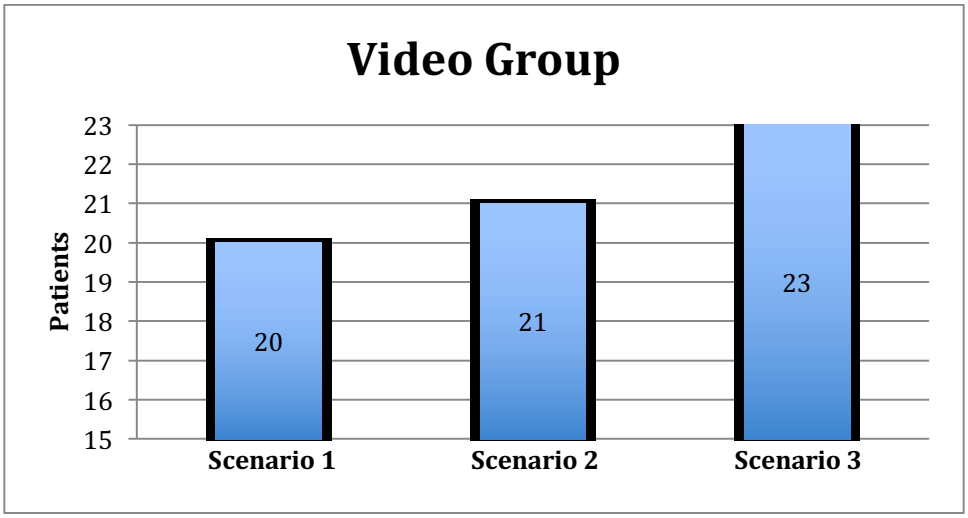


Figure 22: Number of accepters in scenarios 1-3 for the video group

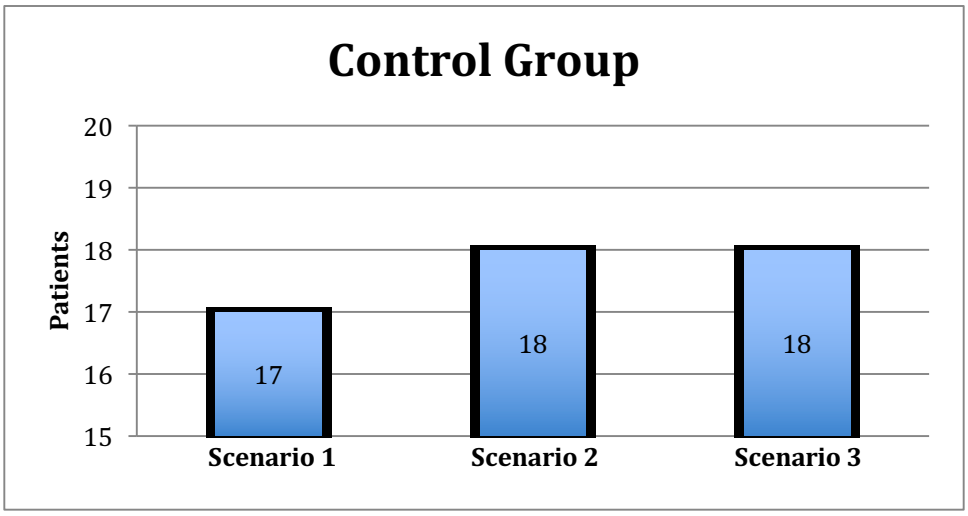


Figure 23: Number of accepters in scenarios 1-3 for the control group

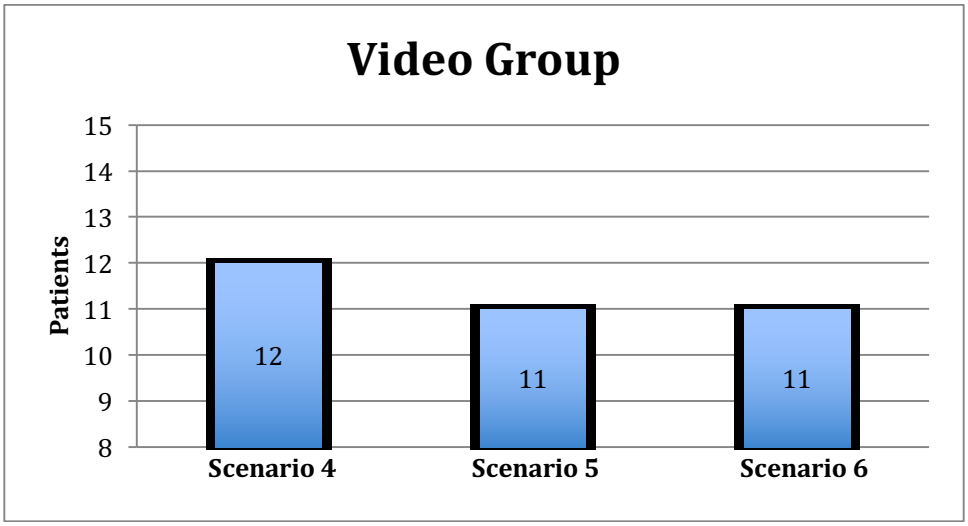


Figure 24: Number of accepters in scenarios 4-6 for the video group

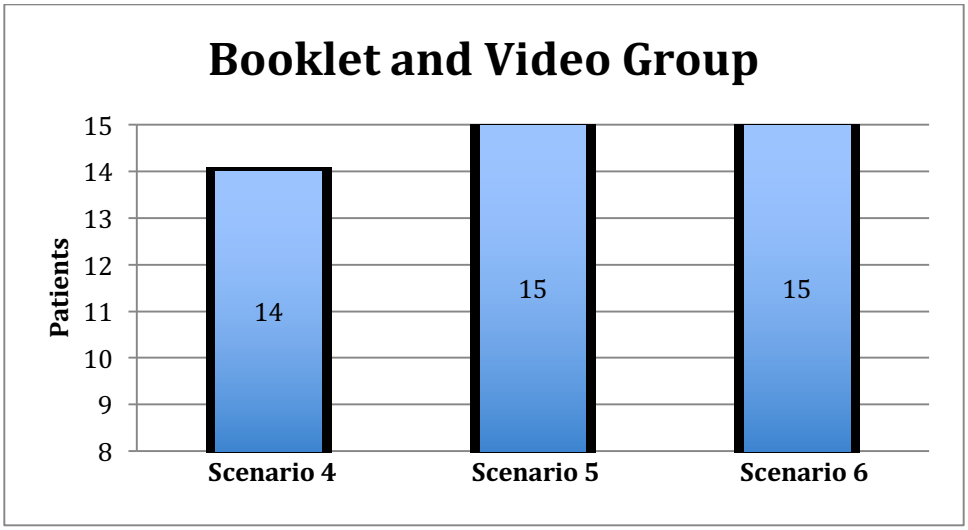


Figure 25: Number of accepters in scenarios 4-6 for the booklet and video group

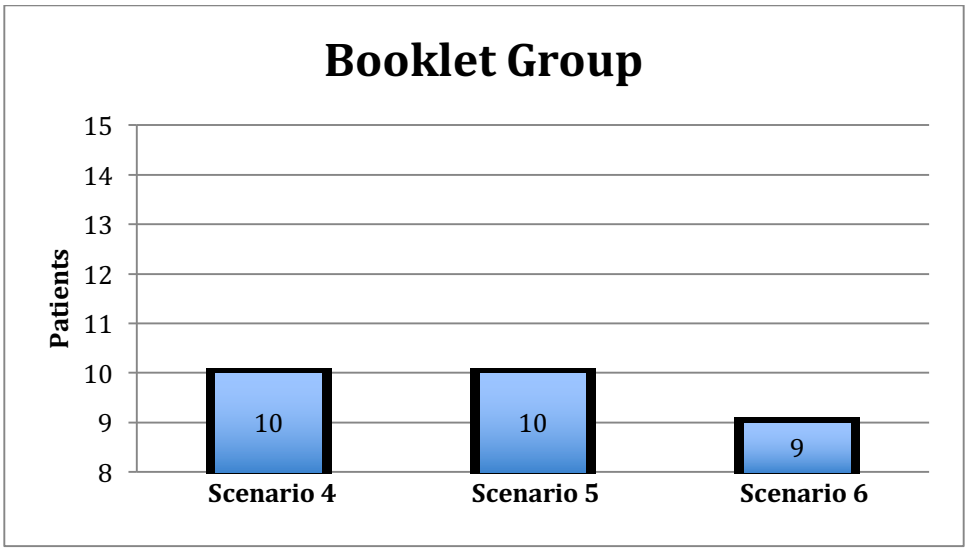


Figure 26: Number of accepters in scenarios 4-6 for the booklet group

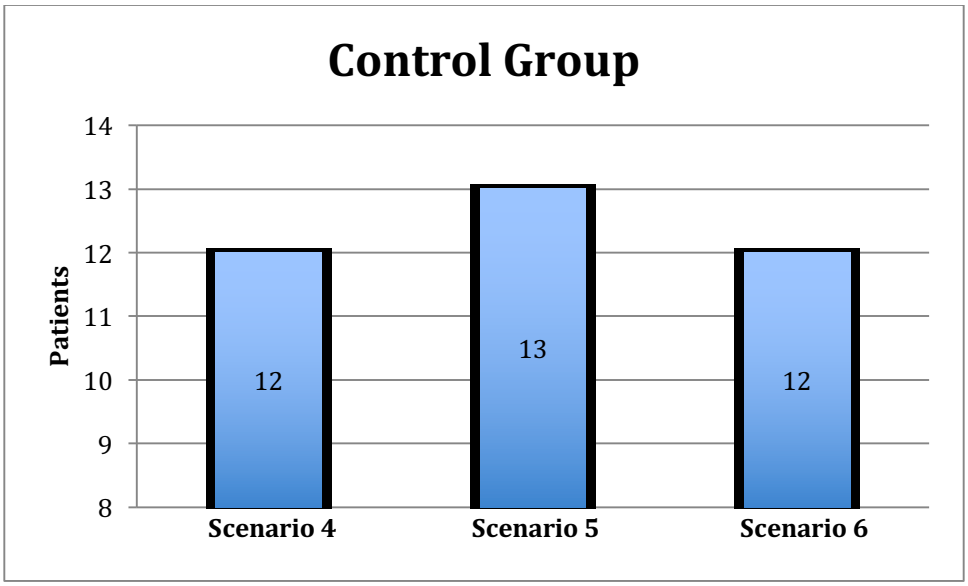


Figure 27: Number of accepters in scenarios 1-3 for the control group

There are some possible explanations for the lack of a positive association between the increase in the allocation ratio and the number of accepters. First, altruism is a reason for patient participation in clinical trials.[28,30,32,33,34,35,36,39] The questionnaire in the present study asked patients to participate in the different scenarios starting with an allocation ratio of 1:1 followed by 2:1 and lastly 3:1. Therefore, if a patient accepted participation in the first scenario with an allocation ratio of 1:1 based on altruism, most likely would not be influenced by the increase in the allocation ratio. As a result, the increase in the allocation ratio would not affect the patient willingness of participation.

Second, the terms used in clinical trials are often not well comprehended by patients. For example, the term "randomization" is not well understood by many patients.[21] A systematic review by Edwards et al.[85] acknowledged that participants in clinical trials often fail to understand that their treatment was selected randomly from among those under comparison. Therefore, it is possible that patients included in this study did not fully understand the concept of allocation ratio, which lead to the findings.

Moreover, there are other possible reasons related mainly to scenarios 4, 5 and 6. In those scenarios, patients were asked to be part of a hypothetical trial with a study drug or a placebo alone and for a one-month period. First, scenarios 4, 5 and 6 asked patients to give up their current medication. Therefore, it is quite possible that patients prefer not to participate, especially if their current medication works well. Six patients reported as a reason for declining participation in a future clinical trial

because their current medication works well. Another possible reason is the short period of time presented in these scenarios. This study hypothesized that if patients are offered the option to give up their current medication for a very short period time that would increase their likelihood to participate. Four patients reported as a reason to decline a future clinical trial is the short time design of the proposed scenarios. Below are samples of answers from these patients:

Patient 1: *"… I am skeptical of what is to be gained from a one-month trial*."

Patient 2: "*A one-month study is not long enough to be effective for results. One year is better.*"

Patient 3: "*Too short time and dangerous to do without needed medicines.*"

Overall, the interventional groups had more patients willing to participate in the given scenarios. These numbers, however, were not significant. There are some possible reasons for the insignificant results. First, it is difficult to predict the effectiveness of any intervention to improve patient recruitment in clinical trials. In a review conducted by Treweek and colleagues [86], only 20 interventions out of 45 had significant results.

Second, there are many factors that play a role in the process of patient recruitment. These factors are related to physicians, logistics and trial design. For example, Avis and colleagues [87] reported that physician recommendation increased the odds for women with breast cancer to participate in a proposed trial and 81% of the accepting women were in favor of the physician recommendation (OR= 2.00, 95%

C. I= 1.00 to 4.01). Therefore, the recruitment process goes beyond using only patient educational interventions.

Third, the sample size for the current study was calculated based on the primary objective of the study, which was to examine patient knowledge score. Patient willingness to participate was a secondary objective. Therefore, in order to detect a significant difference among the groups, the required sample size would need to be larger. Using the results from scenario 1 (an acceptance rate of 62.9% in the control group and 74% in the interventional groups combined) the required number of patients would be 292 patients per group, which is about 10 times the number who participated in this study. Alternatively, a redesign of the interventions and questionnaire might increase the differences in the interventions and decrease the random variance in responses, so that a more feasible sample size would be able to distinguish significant differences from the control group. We note that the willingness to participate questions were very brief and may have left some participants wanting additional details prior to making a decision about participation. Lastly, the process of the current study did not allow patients to have more time to consider the participation nor allow them to discuss that with family members or friends which might have affected their decision.

Some patient characteristics were related to the increase in the willingness to participate in placebo-controlled trials. Further analysis was done to compare some of these characteristics between accepters and decliners, regardless of their study group (using scenario 1 as the main scenario). Table 75 shows a comparison of patient characteristics between accepters and decliners.

Table 75. Comparison between accepters and decliners based on scenario 1.

A) Patients from the control are included			
Patient Characteristic	**Accepters (n=76)**	**Decliners (n=32)**	**P value**
Age	57.68	53.09	**0.07**
Perceived Severity	1.53	1.48	0.84
Perceived Susceptibility	0.72	0.93	0.83
Perceived Barriers	1.84	1.13	< **0.01**
Perceived Benefits	2.09	1.47	< **0.01**
Knowledge Score	9.34	9.00	0.15
Education: Less than high school High school College Graduate	2 25 30 19	3 15 10 4	0.14
Previous Participation in a clinical trial (Yes)	27 (35.5%)	3 (9.3%)	**< 0.01**
B) Patients from the control group are excluded			
Patient Characteristic	**Accepters (n=59)**	**Decliners (n=22)**	**P value**
Age	57.10	51.41	**0.04**
Perceived Severity	1.45	1.54	0.75
Perceived Susceptibility	0.65	0.97	0.36
Perceived Barriers	2.07	1.37	< **0.01**
Perceived Benefits	2.10	1.54	< **0.01**
Education Less than high school High school College Graduate	 2 17 23 17	 1 12 6 3	0.16
Knowledge Score	9.63	9.68	0.73
Previous Participation in a clinical trial (Yes)	20 (33.8%)	1 (4.5%)	< **0.01**

Accepters were older compared to decliners. The average age for accepters was 57.68 (±11.07) years compared to 53.09 years old (±12.58) for decliners. This difference was almost statistically significant (p=0.07). This is consistent with other studies in the literature reporting that older patients have a greater tendency to participate in clinical trials.[22]

Accepters had a significant difference related to their perceived benefits score compared to decliners ($p < 0.01$). Accepters had an average score of 2.09 while decliners scored 1.47 points. Similarly, accepters had a higher perceived barriers scores compared to decliners, which means a more positive perception and lower barrier to participating in placebo-controlled clinical trials ($p < 0.01$). Accepters had an average score of 1.84 (±1.09), while decliners had a score of 1.14 (±0.85).

Another interesting patient characteristic was previous participation in clinical trials. There was a significant statistical difference between accepters and decliners related to previous participation in clinical trials ($p < 0.01$). Among accepters, 35.5% (n=27) versus only 9.3% (n= 3) of decliners reported previous participation in clinical trials.

This finding related to previous participation in clinical trials is consistent with previous studies in the literature.[12,87.88,89] For example, Cameron and colleagues [89] reported that all the patients in their study with previous participation experience agreed to join a clinical trial (100% vs. 49.1% for those without previous experience, p= < 0.001). In another study by Jenkins and colleague [88], patients with previous participation had an odds ratio of 2.87 to participate in a clinical trial compared to patients without a prior experience (p=0.01).

Previous participation is represented in this study by the element of self-efficacy from the HBM. Patients with prior experience in research are familiar with the process of informed consent, procedures, visits, and appear to be more knowledgeable compared to patients without research experience. Thus, prior experience encourages patients to participate in future clinical trials.

Furthermore, due to the differences in acceptance between scenario 1 and 4, we conducted an analysis to compare patients' characteristics between scenario 1 accepters and scenario 4 accepters to identify patient characteristics among those who continued to accept scenario 4. Similarly, we compared the decliners for both scenarios 1 and 4 and the decliners for scenario 4 only. This analysis showed that patients who continued to accept scenario 4 compared to patients who accepted scenario 1 only were younger (56.46 vs. 58.03, p=0.55), had a lower perceived susceptibility score (0.66 vs. 1.03, p=0.24) and a lower knowledge score (9.25 vs. 9.33, p=0.72), (Table 76). None of the variables were significantly associated with acceptance of the hypothetical scenarios. Regarding the decliners, patients who declined scenario 1 and 4 had a lower perceived barriers score (1.13 vs. 1.93, $p< 0.01$), a lower perceived benefits score (1.47 vs. 2.22, $p< 0.01$), were less educated (p=0.04) and fewer had previously participated in clinical trials (9.3% vs. 38.23%, $p< 0.01$) compared to patients who declined scenario 4 only (Table 77). This new analysis showed that patients who continued to decline participation regardless the type of the scenario were the patients with less knowledge and had less positive perceptions scores regarding placebo-controlled clinical trials. The new analysis showed also that patients who accepted scenario 1 and declined scenario 4 had a higher knowledge

and a higher perceived benefits score which means that they had a better understanding for clinical trial design and more expectation for medical benefits from participation in placebo-controlled clinical trials.

Table 76. Patients' characteristics between scenario 1 accepters and scenario 1 and 4 accepters

Patient Characteristic	**Accepters for scenario 1 only (n=33)**	**Accepters for scenario 1 and 4 (continuing accepters) (n=48)**	**P value**
Age	58.03	56.46	0.55
Perceived Severity	1.56	1.57	0.96
Perceived Susceptibility	1.03	0.66	0.24
Perceived Barriers	1.96	1.67	0.20
Perceived Benefits	2.21	1.94	0.12
Knowledge Score	9.33	9.25	0.72
Education: Less than high school High school College Graduate	 0 10 12 11	 3 17 20 8	0.19
Previous Participation in a clinical trial (Yes)	13 (39.3%)	15 (31.2%)	0.48

Table 77. Patients' characteristics between scenario 1 and 4 decliners and scenario 4 decliners

Patient Characteristic	Decliners for scenario 1 and 4 (n=32)	Decliners for scenario 4 only (new decliners) (n=34)	P value
Age	53.09	57.74	0.11
Perceived Severity	1.43	1.56	0.75
Perceived Susceptibility	0.93	1.00	0.85
Perceived Barriers	1.13	1.93	< 0.01
Perceived Benefits	1.47	2.22	< 0.01
Knowledge Score	9.00	9.32	0.29
Education: Less than high school High school College Graduate	 3 15 10 4	 0 10 12 12	0.04
Previous Participation in a clinical trial (Yes)	3 (9.3%)	13 (38.23%)	< 0.01

Because this study included patients from three different clinics, we conducted another analysis without including patients from the oncology clinic to due to the different social perceptions and fear regarding cancer in comparison to diabetes or kidney diseases, which might result in lower willingness to accept a clinical trial which included a placebo arm. The results showed that the educational interventions significantly increased patients' knowledge and perceived barriers scores ($p<0.01$). There was no significant difference in patients' willingness among the four groups. These results are similar to the results for the whole sample including

patients from the oncology clinic which indicates that patients from the oncology clinic did not have a different impact on the study outcomes. Table 78 depicts all the results for the study outcomes without the patients from the oncology clinic.

Table 78. Results for the study outcomes excluding patients from the oncology clinic.

Outcome / study group	**The Booklet n=18**	**The video n=18**	**The booklet and video n=18**	**The control n=18**	**P value**
Knowledge score	9.67	9.67	9.67	7.89	**<0.01**
Perceived barriers	1.74	1.96	2.11	1.10	**<0.01**
Perceived benefits	2.00	2.01	1.94	1.72	0.69
Willingness to participate (# of accepters):					
Scenario 1	13	13	14	13	0.97
Scenario 2	14	13	15	12	0.68
Scenario 3	13	15	14	11	0.47
Scenario 4	5	8	9	6	0.50
Scenario 5	5	7	10	7	0.40
Scenario 6	5	7	9	7	0.60

The Relationship between Knowledge, Perception and Willingness:

Patients' knowledge about placebos can influence their willingness to participate in medical research. This study hypothesized that there is a positive association between patients' knowledge related to placebo-controlled clinical trials and patients' perceptions as well as their willingness to participate in future placebo-controlled clinical trials. The results of this study showed that patients' knowledge was not a significant predictor for patient perceived barriers or benefits nor the willingness for participation in clinical trials. Furthermore, there was no significant difference in the knowledge score between the accepters and the decliners.

This finding is consistent with previous research showing that knowledge is not sufficient to affect behavior and that interventions need to go beyond educating

knowledge to patients.[87] Avis and colleagues [87] concluded that knowledge about clinical trials was not related to participation. This finding is consistent also with the findings of Davis and colleagues [87] who found that a booklet improved cancer patients' knowledge about clinical trials but did not affect recruitment.[87] In another study conducted to assess patients' knowledge and beliefs about clinical trials, the authors found that patients' knowledge scores were not correlated with patients' perceptions of clinical trial importance ($r = 0.15$, $p = 0.42$) or safety ($r = 0.01$, $p = 0.95$).[90] In addition, Aronson and colleagues[91] concluded that the difference in knowledge level between patients who accepted participation in a clinical trial and refusers was actually nonsignificant ($p=0.17$). This could be because a patient's knowledge is measured based on correct answers. Thus, they are less prone to subjective responses. Moreover, behaviors are influenced by personal factors and previous experiences. Curbaw and colleagues[91] presented a conceptual model to depict the complicated relationship between knowledge, beliefs, understanding, and behavior (Figure. 28). The model shows that a patient's behavior (acceptance or rejection of clinical trials) is not solely influenced by a patient's clinical trial knowledge.

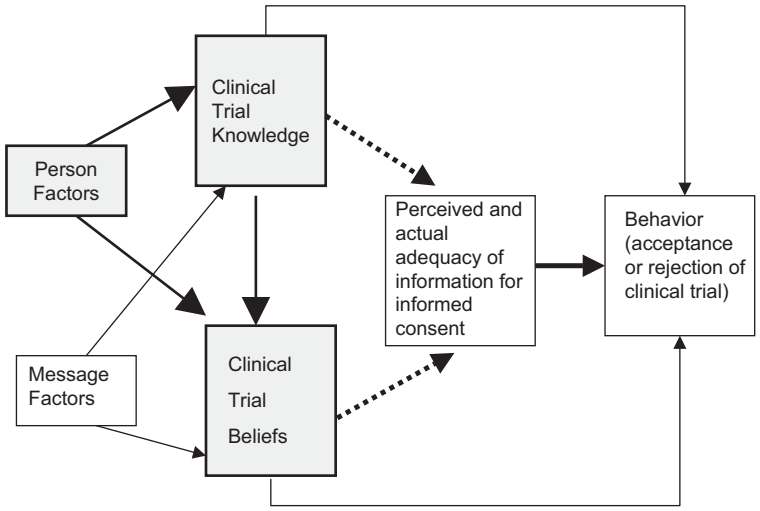


Figure 28: The proposed conceptual model for a patient's knowledge, beliefs and behavior by Curbaw [91]

Moreover, we acknowledge that patients' knowledge about clinical trials can reduce their willingness to participate in them. A previous study conducted by Simes and colleagues [92] concluded that patients with more knowledge related to research aspects were less willing to participate in the offered clinical trial in comparison to patient with less knowledge ($p= 0.01$). The authors discussed the possibility that some patients may experience increased fears as a result of more knowledge about clinical trials. Regardless of what a patient decides, it is important that all patients have a substantial knowledge related to clinical trials and a better comprehension for consent forms in order to make a more informed decision regarding their participation in future clinical trials.

On the contrary, a patient's perceived benefits and barriers seem to be more valuable variables to predict participation in clinical trials. Patients weigh the benefits

and barriers of participation. Then, more benefits and fewer disadvantages or barriers a patient perceives, the greater the possibility that he or she will participate in placebo clinical trials.

The results from this study showed that a patient's perceived barriers and benefits were significant predictors for participation. Patients' perceived barriers and benefits had odds ratios of 2.23 and 2.47 – respectively- for patients' willingness to participate in placebo clinical trials (p= 0.03 and 0.05, respectively). Furthermore, accepters had a significant difference in the perceived barriers and benefits scores compared to decliners.

These findings are similar with other previous studies. In a previous study assessing attitudes toward and willingness to participate in randomized clinical trials of breast cancer treatment, the authors found that women who consider participation reported a greater impact from the positive aspects of clinical trials (OR, 2.2; 95% CI, 1.3 to 3.8) and less impact from the negative aspects of clinical trials (OR, 2.2; 95% CI, 1.3 to 3.2).[56] Another study surveyed women with breast cancer found that 82.7% of the women agreed that potential therapeutic benefits was a personal factor to accept participation in the clinical trial.[87] The same study reported that 94.3% agreed that benefit to others was also a personal factor to accept participation in the clinical trial.

Personal benefits and benefiting others (altruism) were reported as two reasons for patients to participate clinical trials.[28,30,32,33,34,35,36,39] Unlike a patient's knowledge, a patient's benefits and barriers are subjective and more directly related to their health and therefore, can affect patient's perceptions related to clinical trials.

This suggests that more attention should be paid to educating patients about clinical trials benefits and barriers.

The Educational Booklet and Video:

The booklet and the video successfully increased a patient's knowledge and positive perception related to placebo controlled clinical trials. The booklet and the video were designed on the principles of CLT. The incorporation of these principles was very important. Patients included in the study reported that they used a balanced mental effort to read the booklet or watch the video (Neither high nor low mental effort). The patients also rated the booklet as "easy" and the video as "very easy" to understand.

Moreover, some patients noticed that some of these principles were used in the educational materials during the study. Many patients mentioned that using pictures was so helpful. One patient said:

"I have a stroke. My brain is comprehending only simple words and pictures."

Another interesting principle was using the white background in the educational materials. One patient commented:

"Double space and the white background made the booklet easy to read because when you get older it is hard to read".

Another patient said:

"I cannot see colors. The white background helped me to see".

Patients in the video group had slightly a higher score in knowledge compared to the booklet group. This result is consistent with a previous study by Agre and

colleagues.[15] They found that the computer and video consent formats produced slight improvements in understanding over booklet and standard versions (73% vs. 68%, p= N.S). A possible explanation could be that the video format seems to be more engaging than the booklet. Another reason could be that the video incorporated the modality principle. According to the modality principle, the use of video as a communicative device with dynamic images and audio narration, should be superior to print-based text.[60]

In contrast, some patients expressed their preference to the booklet as they were able to read the booklet based on their own pace, unlike the video. Regardless, with the slight differences between the video and the booklet, both interventions were helpful to increase patients' knowledge and perceptions related to placebo–controlled clinical trials.

Study Results and HBM:

The application of the HBM in this study was helpful to have a better understanding for patients' decision to participate in placebo-controlled trials. As the HBM suggests, patients with more perceived susceptibility and severity were more likely to participate in clinical trials. Furthermore, the educational materials used in this study may have provided HBM cues to action by providing them with more knowledge about placebo-controlled clinical trials. These educational materials were used to help patients gain understanding of different aspects of placebo-controlled clinical trials to make informed decisions regarding whether to participate or not. The results of this study are consistent with these components of the HBM model. Patients

from the diabetes clinic had the highest perceived severity and susceptibility scores in comparison with other clinics. As a result, patients from the diabetes clinic had the highest numbers of accepters to participate in the main scenario of this study, although the difference was not significant.

Patients with more perceived benefits and less barriers were more likely to participate in the clinical trial scenarios. Perceived barriers and benefits were significant predictors to accept participation in placebo-controlled clinical trial scenarios. Lastly, the self-efficacy component of the HBM was also supported in this study. Previous participation in clinical trials was another significant predictor of willingness to participate. Previous experiences with clinical trials can provide patients with more experience and confidence which increases their willingness to participate in future studies. Table 79 summarizes the study results and the relevant HBM components related to participation in placebo-controlled clinical trials.

Table 79. HBM components and their relevant to the study results.

HBM Component	Relevant results	Comment
Perceived Severity	Diabetic patients had the highest perceived severity score compared to other clinics. Diabetes: 1.82 Oncology: 1.63 Nephrology: 1.11	The results showed that patients from the diabetes accepters compared to patients from the oncology or nephrology clinic (based on scenario 1). Number of accepters: Diabetes: 28 Oncology: 25 Nephrology: 23
Perceived Susceptibility	Diabetic patients had the highest perceived susceptibility score compared to other clinics. Diabetes: 1.19 Oncology: 0.43 Nephrology:0.73	The results showed that patients from the diabetes accepters compared to patients from the oncology or nephrology clinic (based on scenario 1). Number of accepters: Diabetes: 28 Oncology: 25 Nephrology: 23
Perceived Barriers	Perceived barriers was a significant predictor for participation	OR= 2.27 (p=0.02)
Perceived Benefits	Perceived barriers was a significant predictor for participation	OR= 2.51 (p=0.04)
Cues to Action	The booklet and the video	Increased patients' knowledge, perceived barriers and perceived benefits score compared to the control group.
Self-Efficacy	Previous participation was a significant predictor for participation	OR= 6.71 (p=0.04)

Patients' Reasons for Accepting or Declining Participation in Placebo-Controlled Clinical Trials:

In this study patients shared their reasons to accept or decline participation in placebo-controlled clinical trials. Overall, the reported reasons were similar to what was reported by previous studies.[28-40] More interestingly, four patients reported their reasons to reject participation in placebo-controlled clinical trials was placebo use. Two patients expressed their fear of getting worse if they receive placebo and the other two mentioned that they did not like the odds of receiving placebo. This emphasizes that placebos are seen by patients as a barrier for participation. Researchers should consider more efforts to overcome this barrier.

Moreover, two patients reported that fact that the clinical study is approved and monitored by ethical committees as their reasons for participation. This shows the importance of ethics committees in approving and monitoring clinical trials and expands the role of educational materials to include the ethical aspects of clinical trials.

Study Implications and Future Directions:

The results from this study showed that using educational materials was helpful to increase patients' knowledge about placebo-controlled clinical trials. Providing patients with such educational materials in combination with standard consent forms will allow patients to have a better understanding, reduce their fear and to be able to make a better decisions regarding the participation in future placebo-controlled clinical trials. The use of multimedia is increasing especially with the era of electronic Informed Consent (eIC). The FDA in their guidance defined eIC

as: “using electronic systems and processes that may employ multiple electronic media (e.g., text, graphics, audio, video, podcasts and interactive Web sites, biological recognition devices, and card readers) to convey information related to the study and to obtain and document informed consent”.[93] The availability of such educational materials that contain pictures and multimedia features will be useful to be included within eIC forms using hyperlinks where it is helpful for patients.

Additionally, online recruitment using social media is increasing because it allows researchers the ability to better target their intended audience. In 2012, 81% of adult Americans used the internet, 85% owned a cell phone, and 67% used social networking sites.[94] As a result, the use of eIC will grow as well as the need to have more patient educational materials for online use.

Moreover, the study results indicated that using patient educational materials alone appears not to be sufficient to increase patient recruitment in clinical trials. Another type of intervention such as physician involvement should be included. Lastly, the availability of different forms of educational interventions (printed vs. multimedia) is important to meet patients’ different personal preferences and medical needs.

The findings of this study suggest some recommendations for future research. First, future educational interventions should include the principles from CLT or other similar theories to increase patients’ understanding and reduce cognitive load. Second, using interactive multimedia in future educational materials will keep patients more engaged and can augment evaluation of patients’ knowledge using simple questions and answers. Third, this study examined the impact of using

educational materials on patients' willingness to participate in placebo-controlled clinical trials. Therefore, future studies should evaluate the use of more than one type of patient recruitment strategy. Potential types include different trial designs, consent processes, approaches to participants, financial incentives, and training for recruiters and trial coordinators.

Lastly, future research can examine the impact of using patient educational materials related to placebo-controlled clinical trials in other disease states and using different languages such as Spanish. This will allow more generalizability and the ability to detect any differences in patient behaviors within different disease states or languages.

Strengths and Limitations:

This study has several different strengths. First, the study was randomized which helped reduce selection bias. Second, the study included real patients which can produce more realistic and valid results. Third, the study included patients with three different diseases and from three different clinics which increased the generalizability of the results. Lastly, the study included two different theories, the Health Belief Model (HBM) and Cognitive Load Theory (CLT). HBM was helpful to have a better understanding for patients' perception about placebo-controlled clinical trials. CLT was beneficial to the design of more effective educational materials for patients and reduce their cognitive load.

The study also has some limitations. First, the study measured patients' knowledge at one point of time. Therefore, it is not known of how much patients can

retain after a certain period of time. Future work should involve contacting participants at a future point of time to measure whether their knowledge has been retained. Second, the study used a hypothetical scenario for a placebo-controlled clinical trial to measure patients' willingness for participation. The hypothetical scenario cannot represent the practice in the real world. Offering real clinical trials that include real information about the study procedures, visits, side effects of the study drugs, which can ultimately influence patient decision. Third, the study measured patients' intentions and not the actual behavior. Future studies should include another measurement at another point of time to confirm if patients will translate the intentions into behaviors. Lastly, the process of the current study did not allow patients to have more time to consider the participation nor allow them to discuss that with family members or friends which might also affected their decision.

Conclusions:

The study objective was to design educational interventions to improve a patient's knowledge of placebo controlled clinical trials. The study also measured the impact of the educational interventions on a patient's perceptions (perceived benefits and perceived barriers) related to placebo-controlled clinical trials. And lastly, the study measured the impact of the educational interventions on patients' willingness to participate in placebo controlled clinical trials.

The study results showed that the educational interventions were able to significantly increase patients' knowledge about placebo-controlled clinical trials compared to the control group. Moreover, the educational interventions significantly increased patients' positive perceptions and reduced barriers towards placebo-

controlled clinical trials. Providing patients with such educational materials in combination with standard consent forms will allow patients to have a better understanding about using placebos in clinical trials. The results of this study showed that patients' knowledge was not a significant predictor for patient perceived barriers or benefits nor the willingness for participation in clinical trials. Furthermore, there was no significant difference in the knowledge score between the accepters and the decliners. These findings showed that knowledge is not sufficient to affect behavior and that interventions need to go beyond educating knowledge to patients.

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APPENDICES

Appendix A: The Educational Booklet

Introduction

This booklet provides some information about placebo clinical studies. It aims to help you to understand the meaning of the word placebo. It will also explain to you the following:

- Reasons to use placebos in clinical studies,
- Meaning of the word "Randomization,"
- Ethics of using placebos in clinical studies, and
- Benefits and rights for patients participating in placebo controlled clinical studies.

Now, let us start with explaining the meaning of the word placebo.

1. Meaning of Placebos

The word placebo means: a substance that looks like a real drug but without any active drug in it. A placebo may come in many forms such as a pill, capsule, ointment or injection. An example of a placebo is on the next page.

[redacted]

Placebo Tablet **Study Drug Tablet**

No active drug inside **With active drug inside**

As you can see, it is not easy to differentiate between the real drug and a placebo because they look very similar.

2. Meaning of Placebo Controlled Clinical Studies

A clinical study is a research study to evaluate medical treatments in patients. Clinical studies are very

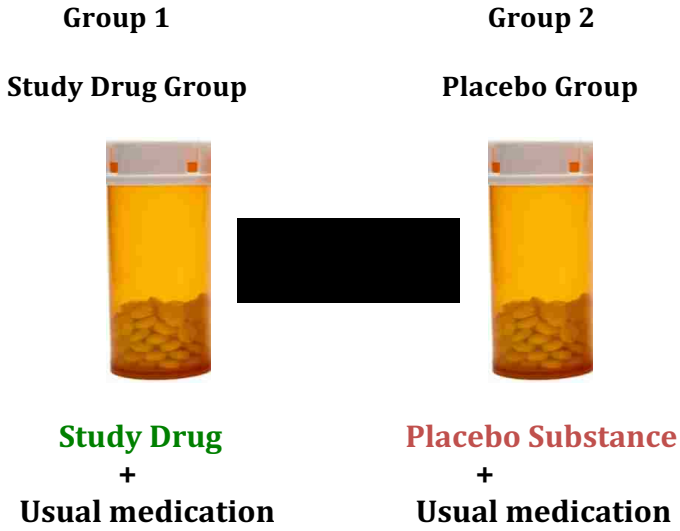
important and most drugs available today were studied in clinical studies. A one type of clinical study is a "Placebo Controlled Clinical Study."

Placebo controlled clinical studies, most of the time include two groups of patients:

* **The first group** is the "**active study drug group."** Patients in this group will take the experimental drug. In order to test the safety of the experimental drug and how well it works, we need to compare it to a control group.

Therefore**, the second group** is the "**placebo control group."** Patients in this group will take the control substance, which is the placebo. The control group (or the placebo group) is used for the sake of comparison with the active study drug group.

In most placebo controlled clinical studies, patients in the placebo group will be given or will continue to take the available usual medications for the same disease under study. Similarly, patients in the study drug group will take the same usual medications in order to have similar study groups for a fair comparison. The picture below explains the most common type of placebo controlled clinical studies.



Since the two groups are similar, patients cannot tell which group they are in. After that, patients will be followed for a certain period of time (few months, a year or two). At the end of the study, the results from each group will be compared to see which group has better results; the study drug group or the placebo group.

3. Reasons to Use Placebos in Clinical Studies

There are scientific and ethical reasons to use placebos in clinical studies. These reasons include exposing fewer numbers of patients to a study or experimental drug and reducing time and cost of a clinical study.

Placebos can be used in clinical studies to serve as a control agent when there is no effective treatment available for a disease or medical condition that can serve as a control drug.

4. Randomization

Randomization is the process by which patients are assigned to one of the two study groups (the study drug or the placebo group) by chance. This means that randomization will assign half of the patients to take the study drug and the other half to take the placebo drug. In other words, there will be one patient assigned to the study drug group and one patient to the placebo group in each randomization process. The picture below explains the process of randomization.

The Randomization Process

In some placebo controlled clinical studies, more patients can be randomized to take the active study drug than patients taking the placebo. For example, giving 2/3 of the patients the study drug and 1/3 of patients the placebo, which means randomizing patients in a 2:1 ratio.

Sometimes even more patients will be randomized to take the study drug and fewer patients to take the placebo like a 3:1 ratio (or 3/4 to 1/4).

5. Ethics of Placebo Controlled Clinical Studies

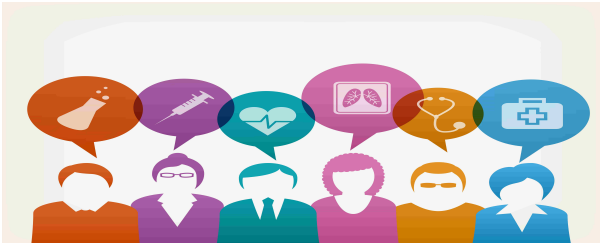
Before any placebo controlled clinical study starts, a special committee called the **Institutional Review Board** will review and approve the ethics of the study.

This committee will protect the rights and welfare of the patients who participate in any clinical study. This committee will make sure that placebos will not be used in clinical studies where:

1- Patients have serious or life threatening illnesses, and

2- Patients will be seriously harmed if they do not receive a real medical treatment for their condition.

There is also another committee called **The Data Monitoring Board.** This committee watches all patients participating in placebo controlled clinical studies. This committee reviews the study data on an on-going basis and makes sure that patients are not harmed by participation in the study.



The Data Monitoring Board is also responsible for stopping a placebo controlled study at any time if the study drug is showing that it works very well and is significantly more effective than a placebo.

6. Patients' Benefits

Patients who are assigned in the study drug group may benefit from taking the study drug. On the other hand,

patients in the placebo control group might not benefit from taking the placebo. However, their participation will provide useful information to help other patients in the future.

By participating in a clinical study, patients may develop some unwanted side effects. For example, some patients may have headache or dry mouth. All patients, however, will be followed closely and monitored for any unwanted side effects. Some other medicines may be given to decrease the symptoms of the unwanted side effects.

Regardless of which group you are in, all patients will get the same medical care and follow up during the study.

7. Patients' Rights

Patients have the right to talk to others (like a family member or a friend) to decide whether to participate or not in a placebo controlled clinical study.

Patients can leave a placebo controlled clinical study at any time and for any reason. The decision to leave a study will not affect the future medical care for any patient.

In summary, let us refresh on the main learning points about placebo clinical studies:

1- Clinical studies are very important to discover and advance new treatments and science,

2- A placebo looks like the study drug but without any active drug in it,

3- It is not easy to tell the study drug from the placebo drug,

4- Patients in the placebo group receive the same medical care identical to patients in the study group,

5- There are scientific and ethical reasons to use placebos in clinical studies,

6- Randomization means that the placebo or the study drug will be chosen for the patient by chance,

7- Institutional Review Board will review and approve the science and ethics of the clinical study and protect the rights and welfare of the patients participating in the study.

8- The Data Monitoring Board is responsible for assuring that patients are not harmed and can stop a clinical study if a study drug is found to be highly effective in comparison to

the placebo drug, 9- For patients with serious or life threatening illnesses, usual medical care is provided in combination to the placebo drug, and

10- You have the right to talk others about your decision to participate or not in a placebo controlled clinical study and you have the right to leave the study at any time, for any reason without affecting your routine medical care.

Conclusion

This booklet is one source to provide you with some basic information about placebo controlled clinical studies. If you would like to learn more or have some questions about placebo controlled clinical studies, please talk to your caregiver in your medical facility at any time.

Learn More about Placebo Controlled Clinical Studies

An Educational Guide for Patients

The University of New Mexico

2015

Study Team

Dennis W. Raisch Mike R. Sather

Matthew Borrego Mark Holdsworth

Khalid F. Al Moaikel

Appendix B: The Educational Video

Please click on the link below.

https://www.youtube.com/watch?v=d53fxyeT-yw&feature=youtu.be

P.S. This video is not available for public on YouTube. You have to use this link it every time to watch it.

Appendix C: Questionnaire form for the Diabetes clinic

A Survey About Clinical Research Studies

Thank you for taking the time to complete this survey. Your responses are very valuable to us. You may need up to 10 minutes to complete this survey. Please start by reading this:

[redacted]

Section 1

Please select the option that best represents you by marking (X) on the appropriate circle:

	1	2	3	4	5	6	7
1- My diabetes is serious.	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
2- I face more life difficulties because of my diabetes.	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
3- My family faces more life difficulties because of my diabetes.	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
4- I worry that my diabetes will get worse.	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
5- I feel I may also get other diseases.	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree

Please Continue to the Next Page >>>

Section 2

>>> Please ask your interviewer for the material about clinical studies that use placebos.

After reading/watching the material about placebo controlled clinical studies and the New Drug study, please answer these two questions:

Please select the option that best represents you by marking (X) on the appropriate circle*:*

1. In reading/watching the educational material I used						
1 ○ Extremely low mental effort	2 ○ Very low mental effort	3 ○ Low mental effort	4 ○ Neither high nor low mental effort	5 ○ High mental effort	6 ○ Very high mental effort	7 ○ Extremely high mental effort

2. How easy or difficult was this educational material to understand?						
1 ○ Extremely easy	2 ○ Very easy	3 ○ Easy	4 ○ Neither easy nor difficult	5 ○ Difficult	6 ○ Very difficult	7 ○ Extremely difficult

Please Continue to the Next Page >>>>>

Section 3

Imagine that your doctor asked if you would like to be in a clinical study to test a drug that may or may not benefit you. Your doctor provided you with the following information about the New Drug study:

Hypothetical Study Background

Your doctor asked if you wanted to be in this clinical study because you have diabetes. The purpose is to obtain information on the safety and effect of an investigational drug. This investigational drug may benefit you and other patients with diabetes. The New Drug is an investigational drug to be taken by mouth that may lower your blood sugar and control your diabetes better than your current drugs.

This study is placebo controlled, which means half of the patients will receive the "New Drug" plus the drugs you take currently for your diabetes. The other half will receive placebo tablets which are "tablets that look like New Drug but without any "active drug". In addition to placebo tablets, patients also will take the drugs that you take currently for diabetes.

The clinical study group will be decided at random, like the flip of a coin. So, if you agree to be in this study, you will be assigned to the New Drug group or the placebo group. In either group you also receive your usual drugs.

This study will last one year. You will be asked to return to the clinic for regular medical checkups.

Some side effects related to the "New Drug" include: decreased appetite, skin rash, headache, dizziness, low blood pressure, and tiredness. Other drugs may be given to treat the side effects. Many side effects go away after the drug is stopped. There may be no benefit to you from this study. But this study will help others in the future.

This is a clinical research study, so your participation is entirely voluntary. If you decide not to be in this study or if you decide to stop being in the study at any time, your care within the UNM clinic will not be change in any harmful way. Your name will be known only to those people who are directly involved in your care for this study. It will not be given in any report of this study.

Please Continue to the Next Page >>>>>

Section 4

Please tell us if you think the following sentences are **TRUE** or **FALSE** based on what you have learned already:

No.	*The sentence*	***TRUE (√)***	***FALSE (X)***
1	A placebo is a substance that looks like the study drug but with active drug in it		
2	Most patients can easily tell if they are taking a placebo from the actual study drug		
3	Randomization means that my treatment will be chosen by chance		
4	Other than the study drug, patients in the placebo group will not get the same medical care as patients in the study drug group		
5	There are ethical and scientific reasons to use placebos in clinical studies		
6	The Institutional Review Board meets before a study begins to make sure that the rights and welfare of patients are protected		
7	The Data Monitoring Board is responsible for stopping a clinical study if the study drug works better and more effective than the placebo		
8	Placebos alone can be given to patients with serious medical conditions		
9	You must not talk to others (family member or a friend) about the clinical study before making your decision whether or not to participate		
10	You can withdraw at any time from clinical studies using placebos		

Please Continue to the Next Page >>>>>

Section 5

Please select the option that best represents your agreement with these statements by marking (X) on the appropriate circle*:*

	1	2	3	4	5	6	7
I am suspicious of placebo controlled clinical studies	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
Placebo controlled clinical studies are not ethical	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
I am confident the group of people who approve placebo controlled clinical studies make sure all participants are treated fairly	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
There may be some medical benefits for me (such as controlling my medical condition and feeling better) if I participate in a placebo controlled clinical study	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
I will still get the same medical care available if I participate in placebo controlled clinical studies	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
There may be medical benefits for other people like me (such as finding new drugs) if I participate in a placebo controlled clinical study	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree

Please Continue to the Next Page >>>>

Section 6

Please answer the following questions:

1- After you have read about the new drug study (the New Drug study), how likely would you join the study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

2- If the study had 2/3 of the patients get the New Drug plus usual medications and 1/3 of patients get the placebo plus usual medications, how likely would you join the New Drug study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

3- If the study had 3/4 of the patients the get the New Drug plus usual medications and 1/4 of patients get the placebo plus usual medications. How likely would you join the New Drug study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

Please Continue to the Next Page >>>>>

4- If the study was done for a short time (one month) instead of a year, and half of the patients got the study drug "The New Drug" alone without taking your usual medications and the other half of patients take placebo alone without taking usual medications, How likely would you join the New Drug study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

5- If the was done for a short time (one month) instead of a year and 2/3 of the patients got the "New Drug" alone without taking your usual medications and 1/3 of patients take placebo alone without taking usual medications, how likely would you join the New Drug study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

6- If the study was done for a short time (one month) instead of a year and 3/4 of the patients the study drug "The New Drug" alone without taking your usual medications and 1/4 of patients take placebo alone without taking usual medications, how likely would you join the New Drug study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

8- In general, please tell us why you would join or refuse to join in a placebo clinical study?

Reasons to Accept	**Reasons to Refuse**
……	……
……	……
……	……
……	……
……	……
……	……

Please Continue to the Next Page >>>>>

Section 7

Please complete the following required information about you

Gender: ○ Male ○ Female **Age**:_____Years

Ethnicity/Race: ○ Non-Hispanic White ○ Hispanic ○ African American ○ Other

Education: ○ Less than High School ○ High School ○ College ○ Graduate School

Marital status: ○ Single ○ Married ○ Divorced ○ Widowed

Estimated Annual Income:

○ Less than $10,000 ○ $10,000 to $25,000 ○ More than $25,000 to less than $40,000

○ $40,000 to less than $55,0000 ○ More than $55,000

Have you ever participated in a research study before?

○ Yes,

○ No

if yes, did the study include placebo group? ○ Yes ○ No

Congratulations, You have completed the survey. Please give it to your interviewer.

Appendix D: Questionnaire form for the oncology clinic

A Survey About Clinical Research Studies

Thank you for taking the time to complete this survey. Your responses are very valuable to us. You may need up to 10 minutes to complete this survey. Please start by reading this:

[redacted]

Section 1

Please select the option that best represents you by marking (X) on the appropriate circle:

	1	2	3	4	5	6	7
1- My cancer is serious.	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
2- I face more life difficulties because of my cancer.	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
3- My family faces more life difficulties because of my cancer.	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
4- I worry that my cancer will get worse	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
5- I feel I may also get other diseases	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree

Please Continue to the Next Page >>>

Section 2

>>> Please ask your interviewer for the material about clinical studies that use placebos.

After reading/watching the material about placebo controlled clinical studies and the New Drug study, please answer these two questions:

Please select the option that best represents you by marking (X) on the appropriate circle*:*

1. In reading/watching the educational material I used						
1 ○	2 ○	3 ○	4 ○	5 ○	6 ○	7 ○
Extremely low mental effort	Very low mental effort	Low mental effort	Neither high nor low mental effort	High mental effort	Very high mental effort	Extremely high mental effort

2. How easy or difficult was this educational material to understand?						
1 ○	2 ○	3 ○	4 ○	5 ○	6 ○	7 ○
Extremely easy	Very easy	Easy	Neither easy nor difficult	Difficult	Very difficult	Extremely difficult

Please Continue to the Next Page >>>>>

Section 3

Imagine that your doctor asked if you would like to be in a clinical study to test a drug that may or may not benefit you. Your doctor provided you with the following information about the New Drug study:

Hypothetical Study Background

Your doctor asked if you wanted to be in this clinical study because you have a cancer. The purpose is to obtain information on the safety and effect of an investigational drug. This investigational drug may benefit you and other patients with cancer. The New Drug is a new investigational drug to be taken orally that might improve your life and might prolong life by extra few months compared to the usual treatment.

This study is placebo controlled, which means half of the patients will receive the "New Drug" plus the drugs you take currently for your diabetes. The other half will receive placebo tablets which are "tablets that look like New Drug but without any "active drug". In addition to placebo tablets, patients also will take the drugs that you take currently for cancer.

The clinical study group will be decided at random, like the flip of a coin. So, if you agree to be in this study, you will be assigned to the New Drug group or the placebo group. In either group you also receive your usual drugs.

This study will last one year. You will be asked to return to the clinic for regular medical checkups.

Some side effects related to the "New Drug" include: decreased appetite, skin rash, headache, dizziness, low blood pressure, and tiredness. Other drugs may be given to treat the side effects. Many side effects go away after the drug is stopped. There may be no benefit to you from this study. But this study will help others in the future.

This is a clinical research study, so your participation is entirely voluntary. If you decide not to be in this study or if you decide to stop being in the study at any time, your care within the UNM clinic will not be change in any harmful way. Your name will be known only to those people who are directly involved in your care for this study. It will not be given in any report of this study.

Please Continue to the Next Page >>>>>

Section 4

Please tell us if you think the following sentences are **TRUE** or **FALSE** based on what you have learned already:

No.	*The sentence*	***TRUE (√)***	***FALSE (X)***
1	A placebo is a substance that looks like the study drug but with active drug in it		
2	Most patients can easily tell if they are taking a placebo from the actual study drug		
3	Randomization means that my treatment will be chosen by chance		
4	Other than the study drug, patients in the placebo group will not get the same medical care as patients in the study drug group		
5	There are ethical and scientific reasons to use placebos in clinical studies		
6	The Institutional Review Board meets before a study begins to make sure that the rights and welfare of patients are protected		
7	The Data Monitoring Board is responsible for stopping a clinical study if the study drug works better and more effective than the placebo		
8	Placebos alone can be given to patients with serious medical conditions		
9	You must not talk to others (family member or a friend) about the clinical study before making your decision whether or not to participate		
10	You can withdraw at any time from clinical studies using placebos		

Please Continue to the Next Page >>>>>

Section 5

Please select the option that best represents your agreement with these statements by marking (X) on the appropriate circle:

	1	2	3	4	5	6	7
I am suspicious of placebo controlled clinical studies	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
Placebo controlled clinical studies are not ethical	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
I am confident the group of people who approve placebo controlled clinical studies make sure all participants are treated fairly	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
There may be some medical benefits for me (such as controlling my medical condition and feeling better) if I participate in a placebo controlled clinical study	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
I will still get the same medical care available if I participate in placebo controlled clinical studies	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
There may be medical benefits for other people like me (such as finding new drugs) if I participate in a placebo controlled clinical study	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree

Please Continue to the Next Page >>>>

Section 6

Please answer the following questions:

1- After you have read about the new drug study (the New Drug study), how likely would you join the study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

2- If the study had 2/3 of the patients get the New Drug plus usual medications and 1/3 of patients get the placebo plus usual medications, how likely would you join the New Drug study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

3- If the study had 3/4 of the patients the get the New Drug plus usual medications and 1/4 of patients get the placebo plus usual medications. How likely would you join the New Drug study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

Please Continue to the Next Page >>>>>

4- If the study was done for a short time (one month) instead of a year, and half of the patients got the study drug "The New Drug" alone without taking your usual medications and the other half of patients take placebo alone without taking usual medications, How likely would you join the New Drug study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

5- If the was done for a short time (one month) instead of a year and 2/3 of the patients got the "New Drug" alone without taking your usual medications and 1/3 of patients take placebo alone without taking usual medications, how likely would you join the New Drug study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

6- If the study was done for a short time (one month) instead of a year and 3/4 of the patients the study drug " The New Drug" alone without taking your usual medications and 1/4 of patients take placebo alone without taking usual medications, how likely would you join the New Drug study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

8- In general, please tell us why you would join or refuse to join in a placebo clinical study?

Reasons to Accept	**Reasons to Refuse**
……..	……..
……..	……..
……..	……..
……..	……..
……..	……..
……..	……..

……..

Please Continue to the Next Page >>>>>

Section 7

Section 7

Please complete the following required information about you

Gender: ○ Male ○ Female **Age**:_____Years

Ethnicity/Race: ○ Non-Hispanic White ○ Hispanic ○ African American ○ Other

Education: ○ Less than High School ○ High School ○ College ○ Graduate School

Marital status: ○ Single ○ Married ○ Divorced ○ Widowed

Estimated Annual Income:

○ Less than $10,000 ○ $10,000 to $25,000 ○ More than $25,000 to less than $40,000

○ $40,000 to less than $55,0000 ○ More than $55,000

Have you ever participated in a research study before?

○ Yes,

○ No

if yes, did the study include placebo group? ○ Yes ○ No

Congratulations, You have completed the survey. Please give it to your interviewer.

Appendix E: Questionnaire form for the nephrology clinic

A Survey About Clinical Research Studies

Thank you for taking the time to complete this survey. Your responses are very valuable to us. You may need up to 10 minutes to complete this survey. Please start by reading this:

[redacted]

Section 1

Please select the option that best represents you by marking (X) on the appropriate circle:

	1	2	3	4	5	6	7
1- My kidney problem is serious.	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
2- I face more life difficulties because of my kidney problem.	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
3- My family faces more life difficulties because of my kidney problem	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
4- I worry that kidney problem will get worse	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
5- I feel I may also get other diseases	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree

Please Continue to the Next Page >>>

Section 2

>>> Please ask your interviewer for the material about clinical studies that use placebos.

After reading/watching the material about placebo controlled clinical studies and the New Drug study, please answer these two questions:

Please select the option that best represents you by marking (X) on the appropriate circle:

1. In reading/watching the educational material I used						
1 ○ Extremely low mental effort	2 ○ Very low mental effort	3 ○ Low mental effort	4 ○ Neither high nor low mental effort	5 ○ High mental effort	6 ○ Very high mental effort	7 ○ Extremely high mental effort

2. How easy or difficult was this educational material to understand?						
1 ○ Extremely easy	2 ○ Very easy	3 ○ Easy	4 ○ Neither easy nor difficult	5 ○ Difficult	6 ○ Very difficult	7 ○ Extremely difficult

Please Continue to the Next Page >>>>>

Section 3

Imagine that your doctor asked if you would like to be in a clinical study to test a drug that may or may not benefit you. Your doctor provided you with the following information about the New Drug study:

Hypothetical Study Background

Your doctor asked if you wanted to be in this clinical study because you have kidney problem. The purpose is to obtain information on the safety and effect of an investigational drug. This investigational drug may benefit you and other patients with kidney problems. The New Drug is an investigational drug to be taken by mouth that may help you to control your kidney problem better than your current drugs.

This study is placebo controlled, which means half of the patients will receive the "New Drug" plus the drugs you take currently for your kidney problem. The other half will receive placebo tablets which are "tablets that look like New Drug but without any "active drug". In addition to placebo tablets, patients also will take the drugs that you take currently for your kidney problem.

The clinical study group will be decided at random, like the flip of a coin. So, if you agree to be in this study, you will be assigned to the New Drug group or the placebo group. In either group you also receive your usual drugs.

This study will last one year. You will be asked to return to the clinic for regular medical checkups.

Some side effects related to the "New Drug" include: decreased appetite, skin rash, headache, dizziness, low blood pressure, and tiredness. Other drugs may be given to treat the side effects. Many side effects go away after the drug is stopped. There may be no benefit to you from this study. But this study will help others in the future.

This is a clinical research study, so your participation is entirely voluntary. If you decide not to be in this study or if you decide to stop being in the study at any time, your care within the UNM clinic will not be change in any harmful way. Your name will be known only to those people who are directly involved in your care for this study. It will not be given in any report of this study.

Please Continue to the Next Page >>>>>

Section 4

Please tell us if you think the following sentences are **TRUE** or **FALSE** based on what you have learned already:

No.	*The sentence*	***TRUE (√)***	***FALSE (X)***
1	A placebo is a substance that looks like the study drug but with active drug in it		
2	Most patients can easily tell if they are taking a placebo from the actual study drug		
3	Randomization means that my treatment will be chosen by chance		
4	Other than the study drug, patients in the placebo group will not get the same medical care as patients in the study drug group		
5	There are ethical and scientific reasons to use placebos in clinical studies		
6	The Institutional Review Board meets before a study begins to make sure that the rights and welfare of patients are protected		
7	The Data Monitoring Board is responsible for stopping a clinical study if the study drug works better and more effective than the placebo		
8	Placebos alone can be given to patients with serious medical conditions		
9	You must not talk to others (family member or a friend) about the clinical study before making your decision whether or not to participate		
10	You can withdraw at any time from clinical studies using placebos		

Please Continue to the Next Page >>>>>

Section 5

Please select the option that best represents your agreement with these statements by marking (X) on the appropriate circle:

	1	2	3	4	5	6	7
I am suspicious of placebo controlled clinical studies	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
Placebo controlled clinical studies are not ethical	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
I am confident the group of people who approve placebo controlled clinical studies make sure all participants are treated fairly	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
There may be some medical benefits for me (such as controlling my medical condition and feeling better) if I participate in a placebo controlled clinical study	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
I will still get the same medical care available if I participate in placebo controlled clinical studies	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree
There may be medical benefits for other people like me (such as finding new drugs) if I participate in a placebo controlled clinical study	○ Strongly Disagree	○ Disagree	○ Somewhat Disagree	○ Neither Agree nor Disagree	○ Somewhat Agree	○ Agree	○ Strongly Agree

Please Continue to the Next Page >>>>

Section 6

Please answer the following questions:

1- After you have read about the new drug study (the New Drug study), how likely would you join the study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

2- If the study had 2/3 of the patients get the New Drug plus usual medications and 1/3 of patients get the placebo plus usual medications, how likely would you join the New Drug study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

3- If the study had 3/4 of the patients the get the New Drug plus usual medications and 1/4 of patients get the placebo plus usual medications. How likely would you join the New Drug study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

Please Continue to the Next Page >>>>>

4- If the study was done for a short time (one month) instead of a year, and half of the patients got the study drug "The New Drug" alone without taking your usual medications and the other half of patients take placebo alone without taking usual medications, How likely would you join the New Drug study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

5- If the was done for a short time (one month) instead of a year and 2/3 of the patients got the "New Drug" alone without taking your usual medications and 1/3 of patients take placebo alone without taking usual medications, how likely would you join the New Drug study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

6- If the study was done for a short time (one month) instead of a year and 3/4 of the patients the study drug " The New Drug" alone without taking your usual medications and 1/4 of patients take placebo alone without taking usual medications, how likely would you join the New Drug study?

1	2	3	4	5	6	7
○	○	○	○	○	○	○
High Unlikely	Unlikely	Somewhat Unlikely	Undecided	Somewhat Likely	Likely	High Likely

8- In general, please tell us why you would join or refuse to join in a placebo clinical study?

Reasons to Accept	**Reasons to Refuse**
……	……
……	……
……	……
……	……
……	……
……	……

Please Continue to the Next Page >>>>>

Section 7

Please complete the following required information about you

Gender: ○ Male ○ Female **Age**:_____Years

Ethnicity/Race: ○ Non-Hispanic White ○ Hispanic ○ African American ○ Other

Education: ○ Less than High School ○ High School ○ College ○ Graduate School

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○ Less than $10,000 ○ $10,000 to $25,000 ○ More than $25,000 to less than $40,000

○ $40,000 to less than $55,0000 ○ More than $55,000

Have you ever participated in a research study before?

○ Yes,

○ No

if yes, did the study include placebo group? ○ Yes ○ No

Congratulations, You have completed the survey. Please give it to your interviewer.

Appendix F: UNM IRB Approval Letter

UNM HEALTH SCIENCES CENTER

Human Research Review Committee
Human Research Protections Office

June 1, 2015

Dennis Raisch, PhD
1 University of New Mexico
Albuquerque, NM 87131
5052722130
draisch@salud.unm.edu

Dear Dr. Raisch:

On 5/19/2015, the HRRC reviewed the following submission:

Type of Review:	Initial Study
Title of Study:	Comparing the Effectiveness of Using Educational Pamphlet or Brief Video on Patients' Knowledge, Perceptions and Willingness to Participate in Placebo Controlled Clinical Trials
Investigator:	Dennis Raisch, PhD
Study ID:	15-110
Submission ID:	15-110
Funding:	None
Grant ID:	None
IND, IDE, or HDE:	None
Submission Summary:	Initial Review
Documents Approved:	Study Protocol v05/2015 Consent Form-after modification v05/22/2015 The pamphlet and the video submitted 05/07/2015 The Survey- International Groups v05/22/2015 The Survey- Control Group v05/22/2015
Review Category:	Exempt: Category (2) Research involving the use of educational tests survey procedures, interview procedures, or observation of public behavior.
Determinations/Waivers:	Waived the requirement to obtain a signed Consent form. Signature waived; requires written statement about research. HIPAA Authorization Addendum Not Applicable.
Submission Approval Date:	5/19/2015
Approval End Date:	None
Effective Date:	5/19/2015

The HRRC approved the study from 5/19/2015 to inclusive. If modifications were required to secure approval, the effective date will be later than the approval date. The "Effective Date"

5/19/2015 is the date the HRRC approved your modifications and, in all cases, represents the date study activities may begin.

Because it has been granted exemption, this research is not subject to continuing review.

Please use the consent documents that were approved and stamped by the HRRC. The stamped and approved consents are in a comment within the submission covered by this approval letter.

This determination applies only to the activities described in this submission and does not apply should you make any changes to these documents. If changes are being considered and there are questions about whether HRRC review is needed, please submit a study modification to the HRRC for a determination. A change in the research may disqualify this research from the current review category. You can create a modification by clicking Create Modification / CR within the study.

In conducting this study, you are required to follow the Investigator Manual dated July 31, 2012 (HRP-103), which can be found by navigating to the IRB Library.

Sincerely,

Thomas F. Byrd, MD
HRRC Chair