THE RELATIONSHIP BETWEEN INFORMED CONSENT PRESENTATION STYLES AND PARTICIPANTS' COMPREHENSION IN CLINICAL RESEARCH

by

Amanda L. Beasley

ANDREA DAINES, PhD, Faculty Mentor and Chair

AUTUMN KEEFER, PhD, Committee Member

KERRY GROHMAN, PhD, Committee Member

Elizabeth Koenig, JD, Dean, School of Public Service Leadership

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Abstract

The aim of this study was to investigate the comprehension of Phase I healthy subjects after they either read a standard informed consent form (control group) or viewed and listened to a video with the same information (experimental group). The findings of this study were to be applied to the efforts of clinical research personnel that perform the consenting process with these subjects. The approach to this dissertation was quantitative and experimental. The nonprobability, convenience sampling design was the best for obtaining access to a sample that could fit the inclusion criteria needed to answer the survey questions. The Cognitive Theory of Multimedia Learning suggests that receiving information through two channels, visual and auditory in this case, and incorporating it with previous knowledge improves comprehension. In this study, analysis of the data did not support the hypothesis that comprehension would be higher for the group that viewed the multimedia presentation. On average, participants in the control group (standard informed consent form presentation) scored 15.47 on the Deaconess Informed Consent Comprehension Test, while participants in the experimental group (multimedia informed consent form presentation) scored 14.67 out of a possible 28 points. These two group mean scores were not significantly different. Findings do suggest that informed consent form comprehension was very low on average, regardless of education, age, residence, occupation, gender, or predicted verbal IQ. Further research is needed to understand how to improve comprehension.

Dedication

This dissertation is dedicated to the many people that have helped me get to where I am today. The support of my family and friends has been crucial to my success. I owe a great deal of gratitude to my parents, Barb and Frank Beasley. Without their continued support and admiration, I would not have gone through this process as effectively and successfully as I have. I also want to dedicate this dissertation to Sue Otten, the love of my life. Her continued encouragement, assistance, and kindness helped me get through times when I just didn't want to try anymore.

I want to thank all of the wonderful people that took the time to finish my survey in order to collect the data for this paper. The survey was long and tedious and took quite the effort by the participants. I want to thank my friend, Dr. Alyssa Streller, for her continuous requests for updates, outreaching to obtain participants, and general encouragement throughout this process. My friends have all been there for me. This journey has been challenging and enlightening and I am so lucky to have these people in my life.

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CHAPTER 1. INTRODUCTION

Introduction to the Problem

Informed consent comprehension is a challenging and controversial issue. The informed consent form (ICF) and informed consent (IC) process resulted from continual evaluation and improvement over the last 100 years. The issues healthy subjects face during clinical research are very different than ill or terminal patients making the decision to participate in a clinical research study. Previous studies have been inconclusive when relating comprehension of the IC for healthy subjects in Phase I clinical trials to presentation of IC information. If healthy subjects cannot properly comprehend the IC then it is not ethical to expect those with any sort of impairment (health, mental, etc.) to have sufficient ICF comprehension. This dissertation aimed to evaluate comprehension of the ICF by comparing a standard ICF presentation (paper) to an audio/visual (multimedia) presentation of the same material so that its findings may be applied practically.

The information found during this study can be applied to the larger clinical research community. The main hypothesis tested was whether participants receiving an audio/visual presentation of the ICF had increased comprehension scores over the participants that are presented with a standard paper ICF. This research has many practical implications. Improving participant comprehension of the ICF supports current rules and guidelines that require keeping research participants safe and protected (Minister of Health, 1996). It is possible that, with the confirmation of increased

comprehension via a multimedia presentation of IC, a change in the guidelines regarding the clinical research administrator's role in presenting informed consent could have been justified. This comprehension evaluation was done using a validated instrument to assess healthy subjects' comprehension, as well as demographics questions, following one of the two presentation styles. If the results had shown that the comprehension was significantly higher with the audio/visual presentation of IC then this may have become the standard process for all clinical research subjects. Researchers in the field would then be expected to promote further work on healthy participants' ICF comprehension and the use of audio/visual aids to do so.

The research in this dissertation helped to add to the current body of knowledge on ICF comprehension. Previously completed research had shown that not all forms of IC presentation results in comprehension for all types of people. There have been many studies that evaluated different ICF presentation methods, but only a few studies have been performed on healthy participants (Paris et al., 2007). Moreover, the studies performed in healthy participants were not conclusive. There is no clearly defined way to consistently improve comprehension in healthy participants (Paris et al., 2010; Stunkel et al., 2010). Incorporation of audio/visual information into the presentation has been shown to improve consent form comprehension in vulnerable populations (Palmer, Lanouette, & Jeste, 2012). However, there is limited information available on whether or not these strategies would help healthy participants.

The research conducted also contributed to the ongoing research in human services. Public service leadership combines public safety, public administration, and health care. Clinical research includes these three topics as well since without clinical

research, health care would not have the drugs and devices used today. Additionally, the Federal Drug Administration (FDA) is required to enforce public administration of clinical research in the United States (Sutar, Gawhane, & Tenpe, 2013). Many guidelines and regulations meant to help protect public safety have come from past transgressions such as the Nuremberg Code (Office of Human Research Protections, 1949), the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979), and the Declaration of Helsinki (Carlson, Boyd & Webb, 2004). As a public service leader, the researcher's goal was to better understand the needs of all subjects' comprehension of such a challenging document to make the clinical research field a safer place for the people involved.

Background of the Study

There have been a myriad of research studies carried out on the informed consent process. These studies range from simple suggestions as to why the informed consent process fails to be truly informative to complex projects that involve completely redesigning the IC process while providing example documents. None of the studies helped identify the comprehension and presentation style of the IC for healthy subjects in Phase I clinical trials. Each one of the studies found during the literature review focused on exploring how someone with a disability, a vulnerability, an illness, or an emergency may be able to understand the information given to them during the IC process (Creed-Kanashiro, Oré, Scurrah, Gill, & Penny, 2005; Gwadz et al., 2011; McCarthy et al., 2012: Sowney & Barr, 2007). However, it is not safe to assume that just because someone is healthy they would be able to fully comprehend an ICF presented to them (Rabin &

Tabak, 2006). This dissertation examined ICF comprehension in healthy subjects in Phase I clinical trials.

There are many issues with the current ICF processes. The ICF is long, full of too much information, and difficult to digest (Paris et al., 2010). "As a consequence, doctors who experience the process of providing written information often have the impression that participants do not grasp the appropriate information from the IC document" (Paris et al., 2010, p. 232). Current research studies also demonstrate variable results in improving IC comprehension (Paris et al., 2007). There is a clear problem defined in the literature that the subjects consenting to clinical research do not understand what they are volunteering for. The current methods used to obtain informed consent are not adequate and improvements need to be made (Barrett, 2005). This dissertation identified the issues with previous ICF comprehension research and provided new insight into ICF comprehension in healthy subjects when subjects were given one of two different presentation styles.

A research study looking to examine reader satisfaction and equal comprehension with a short-form ICF concluded that only lower education level was associated with lower comprehension (Stunkel et al., 2010). This was the only concept the authors found that agreed with other research reviewed in the previous study. Contrary to this previous research, it was determined that healthy subjects' comprehension was not skewed by their drive for financial gain or that previous clinical research experience improves IC comprehension (Stunkel et al., 2010). Another study performed with healthy subjects demonstrated a much greater comprehension rate in those subjects that were presented with an ICF with systematic lexico-syntactic (a correlation between word patterns and

their meanings) enhancement over the standard ICF presentation (Paris et al., 2007). Three years later, a follow up study was conducted using the exact same enhancements with patients suffering from diabetes mellitus, stroke, or sleep apnea (Paris et al., 2010). The researchers found that there were no improvements in comprehension using any of the enhancements (Paris et al., 2010). These studies clearly demonstrate that there is a continued debate over which presentation style of the IC makes a consistent improvement in comprehension.

Many models of improved comprehension in current research focus on a community-involvement aspect, so many people get involved to boost understanding (Cohn & Larson, 2007). However, the authors do not clarify if this method works on only those that are considered vulnerable or if this method also works for those healthy subjects in Phase I clinical research. Another study evaluated improvements to ICFs made by using iterative, educational strategy, allowing ample time for processing and discussion, increasing readability and improving design, as well as "teach-to-goal" (Sudore et al., 2006). Finally, a recent study found that the video version of the consent helped maintain consistency in the process as each time the IC is presented, the same information is provided. The study also supported a positive correlation between the video ICF and improved comprehension (Armstrong et al., 2010).

These consistent findings, partnered with a need to conduct more of the studies in healthy subjects, helped define the need for the proposed study. Moreover, Mayer's Cognitive Theory of Multimedia Learning (CTML) was used to guide the dissertation framework. The CTML suggests that people learn better when receiving information in two forms or channels rather the one (Mayer, 2001). This theory is supported by

Armstrong et al.'s (2010) findings, as well as studies completed by Palmer, Cassidy, Dunn, Spira, and Sheikh (2008) and Rowbotham, Astin, Greene, and Cummings (2013). The Palmer et al. study utilized the visual presentation of the actual paper ICF, while a professional read it aloud and demonstrated higher comprehension in Alzheimer patients when compared with the standard presentation. Participants in a clinical research trial demonstrated a significant increase in comprehension when pairing the paper ICF with an interactive iPad consent system that included audio and visual aids (Rowbotham et al., 2013).

CTML argues that the brain does not incorporate the information in a multimedia presentation as a standalone learning experience; it pulls all of the words, pictures, and auditory information in and combines it with past experiences (Mayer, 2001). This aspect of the theory was applied to the current research by incorporating the participants' predicted verbal IQ when comparing the two experimental groups. Demographics such as education, age, and occupation affect the participants' past experiences. The use of audio/visual presentation of the ICF would, therefore, hypothetically improve a subject's ability to comprehend the content, thereby improving public safety and complying with public administration requiring a truly informed consent to participate.

Statement of the Problem

It is not known to what extent, if any, ICF comprehension differs between healthy individuals and ill patients when comparing ICF presentation style. Researchers must obtain consent or assent from children, adults, the elderly, prisoners, the ill, and healthy alike. Each type of person faces challenges understanding a document with medical jargon that describes what will happen to him or her over the course of a trial, what the

risks and benefits are, and what the compensation will be for volunteering. All of this information is supposed to be provided to the participant at an eighth-grade reading level (Minister of Health, 1996). When an investigational product makes it into clinical development, the first several trials must be conducted in healthy, normal people usually from age 18 to 55. What determines normal and healthy is a bit vague, but these people must be kept safe as well.

Informed consent was incorporated approximately 60 years ago, which is much more recent than how long experiments have been made on human subjects. The quality of ICFs has improved over time, usually resulting from hard-learned lessons over the decades. The International Conference on Harmonization (ICH) E6 guidelines define the accommodations that must be made for potential participants who are unable to read, have language barriers, are mentally deficient, or cannot sign for their own consent on the form (Minster of Health, 1996). The phenomenon of comprehension is a challenging one. It is important to incorporate already-validated surveys that will help evaluate the subjects' comprehension of a generic ICF for a fictional study. The results of the survey that tests the subjects' comprehension were examined to help identify the aspects of the ICF that pose a challenge, even for a person that is not considered to be vulnerable.

It is clear from the current research that there are many flaws in the ICF process. There is no indication, after involvement of government requirements, institutional review board reviews, and media attention that there has been any improvement in ICF comprehension over the years even with the changes that have been incorporated (Stepan et al., 2011). Studies have shown that participants are volunteering for clinical research trials without being able to recall critical information from the ICF they signed (Santen,

Rotter, & Hemphill, 2008). Most studies also only consider patients rather than healthy subjects. There is a lack of understanding how these subjects comprehend consent information. The CTML supports providing information through audio and visual presentation. More research must be done to see if this multimedia form of ICF presentation will improve healthy subject comprehension. This will lead to improved ICF standards that medical staff can feel more confident in for their patients.

Purpose of the Study

The purpose of this study was to gain a better understanding of healthy subject comprehension of the ICF through the use of an audio/visual presentation. Although there are several current studies being conducted in the area of ICF comprehension, there is still a gap in understanding comprehension in healthy subjects. Specifically, the use of the audio/visual presentation with the support of CTML has had very limited research for ICF presentation even though it may offer several benefits. Incorporation of audio/visual information into the presentation has been shown to improve consent form comprehension in vulnerable populations (Palmer, Lanouette, & Jeste, 2012). This finding supports additional research in a healthy subject population.

This study evaluated comprehension using the Deaconess Informed Consent Comprehension Test (DICCT) and collected demographic data that helped to estimate participants' predicted verbal intelligence quotient (IQ). This instrument allowed the researcher to control for the demographic variables when comparisons were made between both experimental groups. The results of the demographic questions were calculated into one value, the predicted verbal IQ. This study was quantitative with a nonprobability, convenience sampling design. The convenience sample was determined

to be the best for obtaining access to a sample that would fit the inclusion criteria needed to answer the survey questions. The experimental design allowed for an unbiased evaluation of the comprehension differences between a standard ICF presentation and an audio/visual presentation of the ICF. Past research supports the use of quantitative design as there is a need for statistics to support the findings and to help promote change.

Research performed over the last decade has been in support of change, but with mixed reasons why and how (Armstrong et al., 2010; Paris et al., 2007; Paris et al., 2010). Even after years of the topic being studied, primarily in patients, there are still an overwhelming number of subjects that do not understand the document they are signing (Barrett, 2005). It has been made clear through previous research that education level, consent document complexity, and presentation all effect comprehension (Palmer, Lanouette, & Jeste, 2012; Paris et al., 2007; Stunkel et al., 2010). This study sought to address some of the issues in which research gaps were found by utilizing a research-supported audio/visual presentation of the information contained in the ICF to identify improvement in comprehension for healthy subjects. It was hoped that this research would support the multimedia presentation style, thereby initiating changes to current minimum requirements for the ICF processes. As a result, comprehension would be increased and consequently make clinical research more ethical.

Rationale

Research supports the need for a study such as this one. ICs have become longer and more complex. Currently there is no requirement to prove comprehension of these forms (Rowbotham et al., 2013). Previous research has demonstrated that IC information presented in forms other than paper (i.e. multimedia or Power Point) can be helpful

(Palmer et al., 2008). However, there is limited information available on whether or not these tactics would help with healthy participants. Previous research has provided very little help to understand how to improve comprehension in the average person, or how the IC process should be evaluated in these participants.

A study was conducted on 100 healthy Phase I subjects to confirm if they were capable of a "quality decision" regarding the informed consent and their willingness to volunteer (Rabin & Tabak, 2006, p. 971). Their research stems from assumptions that subjects volunteering for Phase I studies are predetermined to comply with the consent as they are seeking financial gains from their participation, thus rendering their decision questionable (Rabin & Tabak, 2006). The researchers used a quasi-experimental design with a convenience quota sample to obtain 100 subjects over one year. The subjects were already enrolled in a Phase I clinical trial (Rabin & Tabak, 2006). A linear regression model showed that only 35% of the participants made quality decisions in volunteering for the study (Rabin & Tabak, 2006). The percentage demonstrates the need for informed consent improvements even for healthy subjects. An example of the differences in comprehension expectations lies with the two studies conducted by Paris et al. (2007 & 2010). In the first study, the researchers demonstrated a much greater comprehension rate in healthy subjects that were presented with one of two types of enhancement or both enhancements over the standard ICF presentation (Paris et al., 2007). Three years later, they conducted a very similar study using the exact same enhancements with patients with diabetes mellitus, stroke, or sleep apnea and found that there were no improvements in comprehension using any of the enhancements (Paris et al., 2010).

A recent study concluded with the suggestion of moving forward with integrative iPads that allow the subjects to hear, see, and read about the procedure they are about to have (Rowbotham et al., 2013). Additionally, another study proposed moving forward with a cohesive combination of the paper ICF with some other presentation that integrates re-explanations and thought-provoking questions within it so subjects do not feel they are asking stupid questions (Palmer et al., 2008). Researchers also concluded that there is a definite need for improvements through "empirical testing of methods and instruments capable of increasing candidates' relative intake and uptake of relative information" Rabin and Tabak (2006, p. 977). Finally, both Paris et al. (2007 & 2010) studies indicated that there was a need for powered studies that show definitive support for changes in the ICF.

These findings, combined with the CTML, suggest the need for this study. It is evident in the literature that there has been a large amount of research conducted on ICF comprehension in vulnerable populations and very little performed with healthy subjects. There is a need to start with a foundation of understanding healthy subject comprehension (those thought to be the least-plagued by vulnerabilities) before trying to improve comprehension in those that are ill or vulnerable in other ways. Moreover, the use of an audio/visual presentation may improve comprehension when used to present ICF information to healthy subjects.

Research Questions

The research questions formulated for this study were based upon previous questions answered for validity and extrapolated for further advancement of the knowledgebase of ICF comprehension in healthy subjects.

R_1: Do the sample demographic characteristics vary between the control and experimental groups?

a. What are the demographic characteristics of the study sample?

b. Do the experimental groups significantly vary by demographic characteristic (age, gender, occupation, residence, and education level)?

H_0: There will be no difference in the demographic characteristics between the two groups.

H_1: There will be a difference in the demographic characteristics between the two groups.

$R_{2:}$ Does the level of comprehension vary significantly between the control and experimental groups?

H_0: There will be no difference in comprehension of the ICF whether presented as a multimedia presentation or in the written consent.

H_1: There will be higher comprehension from the subjects in the experimental group. The hypothesis will be further tested by examining the demographics of the study samples in general and then between groups.

R_3: Does level of comprehension of the informed consent vary significantly by predicted verbal IQ?

H_0: There will be no relationship between predicted verbal IQ and comprehension.

H_1: The level of comprehension will be higher in those with a higher predicted verbal IQ.

R_4: Does level of comprehension of the informed consent vary significantly by experimental group status after controlling for predicted verbal IQ?

H_0: After controlling for predicted verbal IQ, there will be no comprehension difference found between the control and experimental groups.

H_1: After controlling for predicted verbal IQ, comprehension will be higher in the multimedia ICF presentation group (experimental group).

Significance of the Study

Current research available demonstrates that not all forms of ICF presentation work for all types of people. There are many studies that evaluate methods of possible improvement in patients, but only a few studies performed in healthy participants (Paris et al., 2007). Additionally, the studies performed in healthy participants have not been conclusive. There is no clearly defined way to consistently improve comprehension in healthy participants (Paris et al., 2010; Stunkel et al., 2010). The CMTL explains that information presented both visually and audibly helps to improve comprehension (Mayer, 2001). However, there is limited information available on whether or not these tactics would help with healthy participants. The current literature gap demonstrates a need for a study like this one. An evaluation on healthy subjects was needed to understand if the multimedia presentation (supported by CTML) would increase comprehension, as the researcher hypothesized.

Previous work has demonstrated the Deaconess Informed Consent Comprehension's (DICCT) validity and reliability in 275 subjects through high inter-scorer agreement and high correlation with the two well-established psychometric instruments, WAIS-R and WRAT-R (Miller, O'Donnell, Searight, & Barbarash, 1996).

Following the completion and publication of this dissertation, work on updating the standard in clinical research IC presentation would be the next goal. Researchers could use the same design on a larger sample or incorporate other comprehension scales to confirm the DICCT results (Miller et al., 1996).

Overall, researchers would be able to continue to evaluate if the audio/visual format of the IC improved comprehension by healthy participants. This goal could be accomplished both by surveying the participants about their feelings of understanding (qualitative) as well as the continued use of instruments like the DICCT to evaluate measureable levels of comprehension. Researchers could also begin to use the audio/visual presentation of the ICF with ill patients to evaluate, with the DICCT, comprehension using this same presentation. The impact to the researchers in the field was to promote further work on healthy participants' ICF comprehension and the use of audio/visual aids to do so.

There could have been many practical implications if the research had supported the hypothesis. Improving participant comprehension of the ICF supported the ethical rules and guidelines meant to keep research participants safe and protected (Minister of Health, 1996). If the research promoting the use of a multimedia presentation of IC in healthy subjects had been proven statistically significant, it could have supported a change in the guidelines regarding the clinical research administrator's role in presenting informed consent.

If the results showed that the comprehension was significantly higher with the audio/visual presentation of IC then this could have eventually become the standard process for all clinical research subjects. Furthermore, the guidelines (ICH) could have

been updated to reflect this change. There is a need for more research to take place, and this study helped add to the current knowledgebase. Larger studies utilizing more participants and studies that use different instruments could be used to show reliability and validity in comprehension measurements. The FDA, government, and clinical research administrators across the globe would have wanted to institute these changes. By having subjects that better understand what they are volunteering for, clinical research may become more respected and better understood. Since the results did not support the hypotheses of this study, the evaluation of the possible reasons why are made in future chapters. Some future research suggestions include: a larger sample could be used, changes could be made to the multimedia presentation length or content, or utilizing participants as their own control. Research may also consider that ICF presentation is very personalized and it would be unreasonable to expect practitioners to be able to accommodate all types and the current standard would be continued to be used. Other conclusions were made following data analysis.

Definition of Terms

Phase I Clinical Trials are usually performed in healthy individuals (except for oncology trials) to evaluate safety items such as frequency and severity of adverse events, and how and where the drug is metabolized within the body (U.S. National Institutes of Health, 2013). For this study the healthy subject that qualifies for a standard Phase I study is being considered. This includes both males and females, ages 18 to 55, and with no major health issues that would exclude them from a typical Phase I study.

Informed Consent or *Informed Consent Form* are often used synonymously but do differ slightly. Informed consent is the entire process of teaching a subject about the

potential study they could participate in including reading the ICF, asking and answering questions, talking to the physician, and general education. The ICF is the actual form the subject reads and takes home that must be signed in order to participate in a study.

Verbal Intelligence Quotient (IQ) is based on the calculation of verbal scales by Wechsler (Wechsler Adult Intelligence Scales) that evaluate general knowledge, language, reasoning, and memory skill (Wechsler, 1997). These tests help to show how a person can perform in these areas rather than their capacity to do so. The verbal scale and performance scales make up a person's full scale IQ. Because it is not practical to have every survey participant take an IQ test, this study utilizes the predicted verbal IQ designed by Crawford and Allan.

Predicted verbal IQ equation is utilized in this study to help understand the estimated IQ of the subjects taking the survey. This will allow for control of these factors when evaluating comprehension in both groups. The predicted verbal IQ equation is as follows: 87.24 - (5.08 x occupation) + (1.77 x years of education) + (.17 x age). Crawford, Millar, and Milne utilize predicted verbal IQs when evaluating premorbid IQs when they cannot be obtained directly from the subject. The equation has been shown to be a reliable alternative when comparing actual WAIS-R IQ scores to their predicted verbal IQ scores using regression analysis (Crawford, Millar & Milne, 2001). The authors found previous equations such as Andres Barona's equation inferior in predicting full scale, performance, and verbal IQ (Crawford & Allan, 1997).

The Deaconess informed consent comprehension test (DICCT) "assesses comprehension of informed consent in a standardized manner" (Miller et al., 1994). The DICCT is a 14-question open-ended survey questions that relate to the eight basic

sections of the IC (Miller et al., 1994). The questions are written at an eighth-grade reading level and in layman's terms. The participants could earn up to 28 points for the survey (*0 = incorrect or no answer, 1= correct, but incomplete, 2 = correct & complete*).

Assumptions and Limitations

One theoretical assumption made was that the healthy clinical participants would acquire the information from the ICF by using two channels (audibly and visually) when given the audio/visual presentation and only through one channel with the standard method (visually/reading). The theory assumed that the participants would better absorb the information when presented with more than one channel of information. The CTML is based on three main assumptions: people have auditory and visual channels for processing information; there are limits to the channel's capacity; and filtering, selecting, organizing, and integrating information are all active learning processes (Mayer, 2001).

A topic-specific assumption was made that the IC is not well understood or comprehended. Also, the ICF process is required in all clinical research and the form must meet the requirements of the FDA (in the United States) and the federal guidelines. Ethically, this document should be designed so the person reading it can accurately understand what they are reading in order to be informed enough to volunteer their participation. According to CFR Section 26.116, "The information that is given to the participant or the representative shall be in language understandable to the participant or the representative. No informed consent, whether oral or written, may include any exculpatory language" (Office of Federal Register, 2013). It is clear IC comprehension inefficiencies need improvement, but not all improvements will always work for all people.

Some methodological assumptions of quantitative research included, (a) random assignment to the experimental group equalized participants across demographic variables, (b) use of quantitative standardized surveys supported objectivity, (c) statistical analysis was used, and was hypothesis-based. This method helped control bias by quantitatively evaluating the comprehension of the two groups and comparing them through SPSS to reject or support the initially proposed hypothesis. Positivists strive for sound scientific methods, in which the research is controlled and unbiased (Ponterotto, 2005). Additionally, the researcher had no influence over the data collection and the results were meant to be generalizable to the population.

An assumption that was made about the DICCT is that it was valid and reliable. The standardized scoring method was utilized to evaluate answers to survey questions. Each survey was scored by hand by the researcher and then another scorer evaluated them to confirm scoring was done accurately. A Kappa calculation was done to confirm inter-scorer reliability. When any score dropped below a Kappa level of 0.80, the two scorers met and discussed the scoring discrepancy, thereby maintaining a minimum of a 0.80 Kappa score.

One limitation to the study was the use of the Covance inactive database for the majority of subject selection. The only way for a participant to be in the database was that they completed at least one clinical research Phase I trial previously, were active at previously closed Covance Clinical Research Units, or had not actively participated in a Covance study in the last three years. Although the database had over 50,000 subjects in it to obtain participants, not all subjects had email addresses and some of the emails that

were in the database were no longer active. Due to time and money constraints, the inactive database was intended to be the primary source of potential participants.

Limiting the study to only include participants whose first language is English could be considered a weakness because it limited the generalizability of the results. However, if this study included non-native English speakers, it would have introduced an additional variable that is beyond the scope of this study. This limitation will need to be addressed in a future study that focuses specifically on differences in comprehension for non-native English speakers.

A third limitation is that the study was performed online and was not performed under direct supervision. During a standard consent process, the person would have been in a quiet room with few distractions and would have been concentrating only on the ICF. Taking the survey at home, the participant could have been distracted and less intent on learning the material within the video or typed ICF.

Theoretical Framework

The Cognitive Theory of Multimedia Learning (CTML) is the theory that guided the dissertation topic. There are three cognitive processes in multimedia learning: (a) selecting (applied to incoming verbal and visual information), (b) organizing, and (c) integrating, (Mayer & Moreno, 1998). These processes occur when connections are built between the verbal cues and visual cues using the corresponding information (Mayer & Moreno, 1998). This means the learner incorporates what they are seeing with what they are hearing and builds a better understanding since the information is received in two forms. The learner participates in active processing, attending to the information that is coming in, organizing it into proper mental representations, and incorporating it into their

current knowledge (Mayer, 2009). CTML contests that learning is incorporating what is already known with what is being presented (Mayer, 2009). The adult learner already has a good base of knowledge. By presenting the IC using an audio/visual presentation, the implications of this theory show that there should be a marked increase in compensation scores.

People "learn more deeply from words and pictures than from words alone" (Mayer, 2001, p. 47). The CTML integrates verbal and visual aids in assisting learners with better understanding by incorporating two "channels" rather than one when taking in new information (Mayer, 2001, p. 47). The style of multimedia learning is meant to initiate the most learning possible by taking advantage of humans' ability to receive information through both audio and visual modes (Mayer, 2009). The audio/visual presentation of the ICF should increase subject comprehension more than in those subjects that only read a paper ICF. "Word and pictures…can complement one another and human understanding occurs when learners are able to mentally integrate corresponding pictorial and verbal representations" (Mayer, 2009, p. 7). Their better understanding occurs when they are able to incorporate "meaningful connections" between verbal and visual descriptions (Mayer, 2009, p. 7). One important note is that visual and verbal messages cannot be processed equally (Mayer, 2009).

The CTML covers three types of multimedia learning purposes. Mayer's Information Acquisition pertains to this study as the participant is meant to learn information and absorb it like a student from their teacher (Mayer, 2009). Information provided to a student through just words is unable to be thoroughly learned as the student needs to store each word and be able to incorporate the meaning of the material with their

prior knowledge (Mayer, 2009). This concept directly correlated with the hypothesis that healthy clinical research subjects would better comprehend the audio/visual presentation of the IC than the standard IC. This theory, in combination with the gap in the literature, helped guide the research for the dissertation.

The theory was used in this quantitative study to conduct an unbiased evaluation of the comprehension differences between a standard ICF presentation and the audio/visual presentation of the ICF. The nonprobability, convenience sampling design was the best method for obtaining access to a sample that could fit the inclusion criteria needed to answer the survey questions. Subjects received either a paper ICF or an audio/visual presentation of the same ICF information followed by same survey questions. Questions included demographic questions as well as the DICCT. This quantitative design was preferable due to the number of studies already conducted and amount of information already available on ICF comprehension. The goal of the dissertation was to demonstrate support of the hypothesis that the multimedia presentation of the ICF would illicit higher comprehension scores.

Organization of the Remainder of the Study

The information within this chapter has provided ample evidence that ICF comprehension is poorly understood and needs further exploration. Further, ICF comprehension in healthy subjects has had little research and needs to be evaluated due to this gap. Previous research on ICF comprehension has been primarily performed on ill patients and has produced mixed results on what methods are useful in improving comprehension. Additionally, the research previously conducted on healthy subjects did

not demonstrate a clear answer for what method is best suited for improved comprehension.

This chapter also provided a brief overview of what methods were used in data collection, and analysis and the research questions were identified. Four research questions guided the research and allowed for a statistical evaluation of the data to interpret the presentation style's effect on comprehension score. Furthermore, descriptions of the terms used regularly throughout the paper were defined to aid in understanding and limitations and assumptions of the study were addressed.

The theoretical framework was discussed and many examples were provided as to why the theory should be supported through the research efforts here. The CTML provided a framework for an expected increase in comprehension through the use of a multimedia presentation of the ICF information. The CTML provided support as to why the hypothesis that the multimedia presentation should have resulted in higher comprehension scores through discussion of multiple-channel reception of information. In the next chapter, the past research that has been conducted on this topic will be examined in more detail. In Chapter 3, the methodology will be thoroughly explained as step-by-step procedures are described. Chapter 4 will describe results and findings of the data, and Chapter 5 will discuss the meaning behind these results as well as provide recommendations for future research.

CHAPTER 2. LITERATURE REVIEW

Introduction

This literature review will provide current and relevant research on the topic of IC in clinical research and how presentation style affects comprehension. It will be organized into themes related to the proposed research study. Additionally, information will be provided on how the existing research and the Cognitive Theory of Multimedia Learning (CTML) applies to this topic. Most of the studies discussed below do not identify a consistent relationship between comprehension and presentation style of the ICF for healthy subjects in Phase I clinical trials. If healthy subjects cannot properly comprehend the ICF then it is not ethical to expect those with impairment (health, mental, etc.) to have sufficient ICF comprehension.

The International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP) states that the informed consent is "A [required] process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate" (Minister of Health, 1996, p. 15). The ICF is long, full of too much information, and difficult to digest (Paris et al., 2010). Most personnel that consent subjects feel that the participant does not truly understand the document (Paris et al., 2010). The current techniques that are used to obtain informed consent are not adequate and improvements need to be made to improve informed consent comprehension (Barrett, 2005). With the support of the CTML, more research needs to be performed to show how the IC process can be improved by utilizing an audio/visual format. This gap in the research will be supported through the literature mentioned here, and a synthesis of the

current knowledgebase will be shared. Finally, a justification for the experimental research design will be provided.

Current Issues

Federal regulations control the type of information that should be provided to potential participants, as well as procedures for documenting consent. Other than suggesting that the document is read to the participant, or individuals having a chance to read it themselves before signing it, there is no guidance on how the form should be integrated into the overall consent process (Department of Health and Human Services, 2010). There are many issues with the current ICF. "As a consequence, doctors who experience the process of providing written information often have the impression that participants do not grasp the appropriate information from the IC document" (Paris et al., 2007, p. 232). Current research studies also demonstrate variable results in improving informed consent comprehension (Paris et al., 2007). From this literature, it is clear that subjects consenting to clinical research may not understand what it is they are volunteering to do.

Only 13% of Americans are literate enough to be considered capable of comprehending a standard ICF (Kripalani, Bengtzen, Henderson, & Jacobson, 2008). The authors also concluded that ICFs are written with excessive complexity and at a far-too advanced reading level (Kripalani et al., 2008). Furthermore, researchers have found that a lengthy consent form is inhibiting, and only 30% of cancer patients understand the document for clinical trials they participate in (Stunkel et al., 2010). Cancer patients greatly overestimate the therapeutic possibilities from ICFs and this could be dangerous and unethical (Barrett, 2005). There were findings in the research that included an

association with lower education level and lower comprehension, likely because of reading comprehension skills that increase with education (Stunkel et al., 2010).

Findings during an evaluation of the use of a quiz in HIV patients in Botswana to check for comprehension showed that those with higher education level demonstrated higher comprehension than those with less education (Chaisson, Kass, Chengeta, Mathebula, & Samandari, 2011). The correlation was further supported by the higher comprehension in those patients that took the quiz in English rather than their native language as those that chose the English version also had attained a higher level of education (Chaisson et al., 2011). The authors not only incorporated the concept of education level and comprehension in the study, but also recognized the change in comprehension over time (length of the clinical trial) (Chaisson et al., 2011). However, there was only a quiz to examine comprehension rather than a validated instrument.

In a recent study, hospital inpatients displayed an improved comprehension of shorter consents or those consents paired with a pamphlet about patients' rights (Benatar, Mortimer, Stretton, & Steward, 2012). The study used a randomized approach of patient comprehension while hospitalized, and the ICF was shortened and paired with a secondary document, a booklet, to help improve comprehension. The study, however, had an element of deceit as the subjects were not told they would be answering a questionnaire following the reading of the ICF. Additionally, the ICF had nothing to do with their ailment. Finally, the questionnaire for this study that was used to assess comprehension was not a validated instrument and was not clearly explained within the literature (Benatar et al., 2012). These issues could make it a challenge to extrapolate

results from the study, and did not positively demonstrate the advantages behind their methods.

Another attempt at improving IC comprehension has been through questionnaires and corrective feedback after the consent is read. There has only been a slight improvement in comprehension, and it does not address the outstanding issue with the IC process (Palmer et al., 2008). The researchers integrated five questions within the IC process while reading through it with the patient; these five questions were based on five requirements in the regulations that must be included in an ICF and were most commonly misunderstood (Palmer et al., 2008). The researchers found that the patients' understanding improved and was rated at 88% comprehension following a second explanation (when necessary) (Palmer et al., 2008). However, the study was conducted using patients rather than healthy subjects. The authors also noted that they did not record their consent process and were unable to compute inter-scorer reliability (Palmer et al., 2008). Additionally, the process did not address recall. Since the questions are only discussed during the consent, and not again at the end, there may be no improvement in retaining the information (Palmer et al., 2008).

The themes found in the research of informed consent comprehension directly correlates to the need for further research. Even after years of the topic being studied, primarily in patients, there are still a large number of subjects that do not understand the document they are signing.

> Must investigators disclose and must potential participants understand the scientific design of the study? Do they need to understand that the study is Phase I [conducted in healthy individuals], and how that differs from Phase II [small patient population studies] and Phase III studies [larger patient population]? Some languages do not include a word for research

> and many individuals do not understand concepts fundamental to clinical research, such as the germ theory of disease. (Wendler & Grady, 2008, p. 204)

The goal of an informed consent is two-fold. The potential participant needs to decide that the study is in line with their interests and if they want to enroll (Wendler & Grady, 2008). The ICH guidelines describe the need for the informed consent to protect individuals, both healthy volunteers and patients (Minister of Health, 1996).

There is a struggle to find the right amount and type of information that should be shared with the potential subject. If too little information is given, or the use of "clinical study or trial" is used with people who have never participated in clinical research before, there is likely going to be a lack of understanding (Wendler & Grady, 2008, p. 204). Likewise, explaining all risks and aspects of the study is impractical and nearly impossible (Wendler & Grady, 2008). Clinical researchers have an ethical requirement to strive for ICF comprehension by all participants. The research indicates that there are many issues in both vulnerable populations and healthy subjects. It is clear that education level, consent form complexity, and presentation method all effect comprehension. This information links the current research to the gap identified for the dissertation. Therefore, the research for this study addressed the gap in the literature by focusing on the need for a valid and reliable comprehension instrument, an improved presentation style of IC information, and a sample of healthy subjects to demonstrate the relationship between these components.

Healthy Subject Applications

There is much less research available on healthy subject IC comprehension than IC comprehension by vulnerable or ill patients. One such study was performed in healthy

subjects that volunteered to participate in a Pfizer Phase I clinical research study; the comprehension study was a sub-study conducted over the length of the Pfizer study (Stunkel et al., 2010). The design was an improvement on past studies as "many used consent documents in hypothetical situations rather than in actual research studies" (Stunkel et al., 2010, p. 1). By including actual clinical research subjects in the ICF comprehension trial, the resulting data are more representative of the real-life situation. Subjects in a real clinical research study are more apt to take the consent form more seriously than if they were in a mock study. The authors investigated the comparison of a shorter, easier ICF versus a standard length ICF followed by a questionnaire to assess both comprehension and. The results showed that there were no gender, employment, age, or previous trial experience effects on the subject's comprehension. The only relationship found was a positive correlation between higher education and better comprehension (Stunkel et al., 2010).

Another study was conducted using 100 healthy Phase I subjects to confirm if they were capable of a "quality decision" regarding the informed consent and evaluated their willingness to volunteer for clinical trials (Rabin & Tabak, 2006, p. 971). Their research stemmed from concern that subjects volunteering for Phase I studies had already decided to comply with the consent as they are seeking financial gains from their participation, and this would render their decision questionable (Rabin & Tabak, 2006). The average range of per-visit payments is $50 to $200, depending on procedures performed and complexity (Center for Information & Study on Clinical Research Participation, 2013). The researchers used a quasi-experimental design with a convenience quota sample to obtain 100 subjects over one year while the subjects were

already enrolled into a Phase I clinical trial (Rabin & Tabak, 2006). The design was quasi-experimental due to the sampling method and its non-random sampling of subjects. They did not collect any data from the original intended group of those subjects unwilling to consent to participate in the Phase I clinical trial from which they sampled (Rabin & Tabak, 2006). A linear regression model for the dependent variable 'decision-making' showed that only 35% of the participants made quality decisions in volunteering for the study (Rabin & Tabak, 2006). This was performed using an "inclusion of all variables with forward selection and backward elimination" (Rabin & Tabak, 2006, p. 974). Unfortunately, the authors correlated the high rate of Phase I study volunteers' willingness to participate with the drive for financial gains since only a third of them would truly understand the ICF (Rabin & Tabak, 2006). There are many other factors that would need to be considered before assuming this. The percentage, however, demonstrated the need for informed consent improvements even for healthy subjects.

A good example of the differences in comprehension expectations lies with the two studies conducted by Paris et al. (2007 and 2010). The research demonstrated a much greater comprehension rate in those healthy subjects that were presented with either enhancement or both over the standard ICF presentation; all four groups (two changed ICFs, two unchanged) showed a statistically significant ($p = 0.020$) difference in comprehension scores (Paris et al., 2007). The relationship between the groups pairwise between working and unchanged was also statistically significant ($p = 0.003$) demonstrating a greater comprehension in those ICFs that have been improved upon (Paris et al., 2007). Three years later, Paris et al. (2010) conducted a very similar study using the same ICF enhancements on patients with diabetes mellitus, stroke, or sleep

apnea and found that there were no improvements in comprehension using any of the enhancements. The same statistics showed a *p* value of only 0.38 and only approximately a two-point difference in comprehension scores between the working group ICFs and the unchanged ones (Paris et al., 2010). These two studies demonstrated a distinct difference between healthy subject and ill patient comprehension. This difference needs to be better understood and accommodated.

When considering healthy participants there are many characteristics that any healthy individual has that can affect their ability to comprehend and understand things in their day-to-day lives. To clarify, occupation, education, age, and gender (ordered from greatest to least affect) have been known to affect verbal IQ (Crawford & Allan, 1997). IQ has been shown to have a positive correlation with reading comprehension (Tiu, Thompson, & Lewis, 2003). The Crawford and Allan predicted IQ equation is a validated tool that incorporates all of these elements into estimating the full scale IQ, performance IQ, or verbal IQ when a true calculation is not available (Crawford & Allan, 1997). These basic demographics are the essence of a person, regardless of their health. These demographics were taken in consideration when evaluating comprehension levels in the healthy subjects.

It has been cited many times that there are no gender differences in IQ. However in 2006, a study showed that, on average, men tested 3.63 IQ points higher than their female counterparts (Jackson & Rushton, 2006). Their findings were based on two observations – differences in mental ability and a gender difference in brain size (Jackson & Rushton, 2006). Additionally, the authors found racial differences between black and white people, a consistent finding when approaching it genetically and environmentally

(Rushton & Jensen, 2005). Consistently, IQ was lower in black people than in white people, and while this finding was controversial it was supported by several different studies evaluated and performed (Rushton & Jensen, 2005). Another researcher counters that the Rushton & Jensen findings are not properly cited and unsupported; his findings show that the differences (hereditarily or environmentally) are "nil" (Nisbett, 2005, p. 302). Other studies have shown a positive correlation between education level and higher IQ in later life. There was strong association with those with lower IQs before education and their later-in-life IQ scores (Ritchie, Bates, Der, Starr & Deary, 2013). These concepts were further evaluated during the application of Crawford and Allan's equation for predicted verbal IQ to the scoring of the comprehension test.

It is evident through the literature review that there are many articles written about ICF comprehension in vulnerable populations and very little written about healthy subjects. Clinical researchers need to start with a foundation of healthy subject comprehension before trying to understand comprehension in those that are ill or vulnerable in other ways.

Methodology

The methodology used to collect and interpret the information was a quantitative study including nonprobability sampling design. Specifically, the convenience sampling method was used. The sample included those participants willing to participate in an online survey following either a standard ICF presentation or an audio/visual presentation of the same ICF. The ICF used for this study was a "mock" ICF that included the average number of procedures, blood draws, and risks to a healthy subject in a Phase I clinical trial (see Appendix A).

The Deaconess Informed Consent Comprehension Test (DICCT) was used to evaluate comprehension (Miller, O'Donnell, Searight, & Barbarash, 1996) and a basic demographics survey was provided. The DICCT allowed for comprehension assessment using a standardized tool (Miller et al., 1994). The DICCT was tested by correlating the instrument with two psychometrically established measures (WAIS-R and WRAT-R) to see if it validly demonstrated participants' comprehension of the informed consent (Miller et al., 1994). The test showed high validity and reliability in demonstrating this. The DICCT was tested using 275 healthy educated participants rather than geriatric and ill participants which previous researchers have used, which ends up with inconsistent data (Miller et al., 1994). "Studies have increased numerically during the past decade, but investigation in this area has been hindered by methodologic and conceptual issues" (Miller et al., 1994, p. 877).

The DICCT is a 14-question open-ended survey questions that relate to the eight basic sections of the IC (Miller et al., 1994). The questions are written at an eighth-grade reading level and in layman's terms. The participants could earn up to 28 points for the survey (*0 = incorrect or no answer, 1 = correct, but incomplete, 2 = correct & complete*); the survey was read aloud to the participant and answers were provided verbally (Miller et al., 1994). A mean score of 21.94 ± 3.17 equates to good comprehension (Miller et al., 1994).

Appropriate descriptive statistics were used to evaluate the demographics results. Analysis of Covariance was used to test group differences in comprehension level after adding the predicted verbal IQ as a covariate as supported by Crawford and Allan (1997). By calculating the predicted verbal IQ, the analysis was based on comparing the group

verbal IQ estimates to their ability to comprehend the ICF presentations. Differences in level of comprehension by experimental groups were tested using independent samples *t*-tests. Information such as the basic comprehension comparison of the two types of delivery were made, as well as demographic characteristics such as differences in gender, age, education level, and occupation. This type of analysis allowed for between-groups comparisons.

The decision to conduct a quantitative study was based on the current research being strongly quantitative. There is already a basic understanding of informed consent comprehension, and there is little need to further investigate qualitative research in this area. Many of the aforementioned studies used quantitative methods to help evaluate different delivery methods, forms, satisfaction, etc. in patients with only a few studies conducted in healthy subjects. The research method used here should provide further evidence that the method of ICF delivery effects comprehension and will add to the current knowledgebase. Furthermore, if the study had found a positive correlation between the audio/visual presentation and comprehension then these data would have supported the need to improve upon the current standard recommended by the ICH guidelines as well as the Code of Federal Regulations.

Theoretical Framework

"Effective use of technology may provide new ways for physicians to communicate with their patients more efficiently" (Armstrong et al., 2010). People "learn more deeply from words and pictures than from words alone" (Mayer, 2001, p. 47). Mayer and Moreno clarify that this does not mean to simply add words to pictures will directly improve meaning and understanding (1998). This is the core concept behind

the Cognitive Theory of Multimedia Learning (CTML), the theory that guided the dissertation. The authors explain that there are three cognitive processes in multimedia learning: selecting (applied to incoming verbal and visual information), organizing, and integrating, which occur when the learner makes connections between corresponding events in the verbal communication and the visual communication (Mayer & Moreno, 1998). The brain does not receive visual and auditory signals as singular events, but rather incorporates the new information with what is already known (Mayer, 2001).

The CTML integrates verbal and visual aids in assisting learners with better understanding by incorporating two "channels" rather than one when taking in new information. The use of video-based informed consent in skin biopsy patients demonstrated these findings empirically. A statistically significant increased knowledge score of 1.55 ± 1.71 points (mean ± SD; 95% CI for increase 1.01 – 2.08) was found in those who watched a video version rather than the standard verbal education of the ICF (Armstrong et al., 2010). The authors also found that the video version of the consent helped maintain consistency in the process as each time it was presented it was the same information being provided (Armstrong et al., 2010). Moreover, there was no decrease in satisfaction in watching the video rather than hearing the information from the doctor (Armstrong et al., 2010). The authors were concerned the video would be impersonal and would lower satisfaction (Armstrong et al., 2010).

Another study evaluated 20 different studies that involved the use of multimedia aids in informed consent processes. The researchers found that the large majority of the studies evaluated it in patients (primarily cancer and psychoses patients), much like other ICF comprehension studies that have been discussed above (Palmer, Lanouette, & Jeste,

2012). Their findings, however, were very supportive of the use of multimedia in the ICF process. The researchers found that 50% (10 studies) of the studies showed a significant increase in comprehension, 30% (six studies) had partial improvement in comprehension, and only 20% (four studies) had an insignificant change in comprehension (Palmer et al., 2012). This concept directly correlates with the hypothesis that healthy clinical research subjects will better comprehend the audio/visual presentation of the informed consent than the standard informed consent

Possible Improvements

Many researchers are attempting to find ways to improve the ICF. This can be through changing the length of the document, presenting it in different ways, giving the subjects extra time to understand it, among others. Many models of improved comprehension are coming from a community involvement aspect, in which family and community members get involved to improve understanding (Cohn & Larson, 2007). The authors do not clarify if this method works on only those that are considered vulnerable or if this method also works for those healthy subjects in Phase I clinical research. "Some preliminary and small studies suggest that decreasing the length and complexity of consent forms may improve understanding, satisfaction with the informed consent process, or both" (Stunkel et al., 2010, p. 1). Their research demonstrated that the length of the form has no bearing on IC comprehension, or even, satisfaction. Short or long, the subjects are no more satisfied and have no statistically different changes in comprehension (Stunkel et al., 2010). Additionally, they did find that those subjects that volunteered for Phase I studies for the purpose of monetary gain did, indeed, have better comprehension than those participating for other reasons (Stunkel et al., 2010).

Researchers attempted to design different ICFs that could be tested for a change in comprehension (Paris et al., 2007). They performed a randomized control study to evaluate an "unchanged ICF, ICF with Systematic Lexico-syntactic Readability Improvement (SLRI), ICF modified by a working group and one that was modified and followed by SLRI" (Paris et al, 2007, p. 209). Their analysis using ANOVA did show differences between the four groups that supports the research for this dissertation. "The pairwise analysis showed improvement in the ICF modified by a working group compared to the unchanged ICF ($p = 0.003$) as well as an improvement in the group reading the SLRI modified ICF ($p = 0.020$) and the ICF with both the working group and SLRI modifications ($p = 0.027$)" (Paris et al., 2007, p. 209).

Improvements to ICFs can be made by using iterative, educational strategy, allowing ample time for processing and discussion, increasing readability and improving design, as well as "teach-to-goal" (Sudore et al., 2006, p. 867). There were 329 subjects assessed to confirm if the teach-to-goal model of ICF presentation improved comprehension (from 28% with complete comprehension on first pass to 98% by a third pass) (Sudore et al., 2006). The study also found race, ethnicity, and literacy level to have a great effect on the number of passes need prior to achieving complete comprehension (Sudore et al., 2006). Unfortunately, the study was conducted only in vulnerable subjects and was not extrapolated into healthy subjects.

The above research has suggested and tested several different possible improvements to the ICF. Researchers found a relationship between race, ethnicity, and literacy level and the ability to comprehend the ICF (Sudore et al., 2006). They approached the comprehension improvement by utilizing repeated passes (Sudore et al.,

2006). Although it appears it worked, this could take much time that may not be available to clinical research personnel. Other research found modifications to the ICF to improve comprehension. Furthermore, a study showed that by incorporating a multi-faceted presentation of a video introduction, the standard consent, and a tablet-based quiz improves comprehension (Rowbotham et al., 2013). The study looked at integrating reading, seeing, hearing, and interacting with learning materials and the ICF and how that would improve comprehension (Rowbotham at al., 2013). Their findings supported the benefits of CTML similar to what this dissertation aimed to find. The dissertation sought to identify an improvement in ICF delivery that increased subject comprehension supported by the CMTL.

Conclusion

The literature review provided here set a foundation to the informed consent comprehension dilemma. There is much room for improvement, both in healthy subjects and vulnerable populations. The literature indicated that there has been research done on informed consent comprehension, but there is much more to be done in healthy subjects. It is evident that things such as verbal IQ, demographics, presentation style, and consideration of a combination of these all greatly affect the comprehension level of the reader. With the guidance of the Cognitive Theory of Multimedia Learning and the use of healthy subjects, this study investigated the relationship between comprehension and the presentation style of the informed consent document. The researcher hoped to support the idea that the audio/visual presentation of the IC demonstrated improved comprehension over the current standard IC presentation.

CHAPTER 3. METHODOLOGY

Research Design

Logical positivism (LP) relates to the hypothetico-deductive method and should incorporate empirical data and utilize supported (or not) hypotheses that lead to theory development (Ponterotto, 2005). Logical Positivism is objective, relies on the data, utilizes available instruments to measure the data, and is considered to be more credible by the scientific community than interpretivism. The quantitative design was chosen for this study to align with the LP approach to research. Crossan (2003) suggests that positivism is defined by hard facts and their relationship to scientific laws. There are many advantages to using this type of lens when researching topics of concrete experimental potential. In other words, the use of LP and quantitative approaches to all fields is advantageous to demonstrate the trends and defined factors behind a concept. The assumptions of LP helped to define the methodology chosen to evaluate ICF comprehension in this dissertation.

The approach to this dissertation was quantitative and experimental. The nonprobability, convenience sampling design was the best method for obtaining a sample that could fit the inclusion criteria needed to answer the survey questions. The experimental design allowed for an evaluation with the least amount of bias possible of the comprehension differences between a standard ICF presentation and the audio/visual presentation of the ICF. Previous literature demonstrated a clear understanding of the basics of ICF comprehension (Cohn & Larson, 2007). Previous studies have already utilized qualitative approaches to understand subject comprehension of ICFs (Azotam,

2012; Deal Poston, 2012; Griffiths & Harmon, 2011), and it was determined for this study that a quantitative design would allow the findings to best contribute to the existing literature. Collecting quantitative data and using statistical analysis to evaluate ICF presentation styles will contribute to improved clinical research subject safety. By providing statistical evidence in support of changes, ICF comprehension could be improved on a more global level through changed regulations and guidelines. By using experimental design, the differences in comprehension levels between a current accepted standard versus the new suggested approach were evaluated. The internal validity of the study was greatly increased by the use of both an experimental group and a control group. When only one group is used, internal validity is low (Rubin, 2010).

The variables in the study were chosen based on the calculation of the predicted verbal IQ of the participant as well as the DICCT. The predicted verbal IQ is an estimate easily obtained without requiring an IQ test by using demographic data (Crawford & Allan, 1997). This helped account for basic differences in comprehension and control for these variables when making comparisons between both experimental groups. The dependent variable and seven independent variables are all related to the Cognitive Theory of Multimedia Learning. The relationship of the variables and the theory appear in Table 1.

Table 1

Variables and the Link to the Cognitive Theory of Multimedia Learning

Variable Name	Link to Cognitive Theory of Multimedia Learning
Comprehension level (Dependent)	CTML suggests an increase in comprehension in the experimental group since there is both audio and visual presentation. Therefore participants in experimental group should obtain higher DICCT scores than those in the control group.
IC presentation style (Independent)	The theory states that "people learn more deeply from words and pictures than from words alone" (Mayer, 2001, p. 47). Therefore, the experimental design incorporates the audio/visual type of presentation for the experimental group and standard ICF (reading) presentation for the control group.
Age (Independent)	Age contributes to one of the five processes of the CTML, meshing the verbal and pictorial representations with each other and with what is already known (Mayer, 2001). This prior knowledge is gained over the years as each person experiences life. The older the person, the more comprehension they should have.
Race (Independent)	"Learner pays attention to relevant words in a multimedia message to create sounds in working memory (selecting images) and they also build connections between verbal and pictorial models and with prior knowledge (integrating)" (Mayer, 2001, p. 41). There are cultural differences between races in how images are viewed, as well as how they are connected to the words they hear. This information will then be integrated into previous knowledge differently across the races. This may affect scores across the different races.
Gender (Independent)	"Learner builds connections among selected images to create a coherent pictorial model in working memory" (Mayer, 2001, p. 41). This image organization is part of CTML. How men and women organize images differs. There should be a difference in their scores.
Education level (Independent)	Education level contributes to one of the five processes of the CTML, meshing the verbal and pictorial representations with each other and with what is already known (Mayer, 2001). This prior knowledge is gained during our education. The more education the person has, the higher their comprehension should be.
Residence (Independent)	"Learner pays attention to relevant words in a multimedia message to create sounds in working memory (selecting images) and they also build connections between verbal and pictorial models and with prior knowledge (integrating)" (Mayer, 2001, p. 41). There are cultural differences between urban/rural residences in how images are viewed, as well as how they are connected to the words they hear. This information will then be integrated into previous knowledge differently across the residences and may result in different scores between urban and rural subjects.
Occupation (Independent)	Occupation contributes to one of the five processes of the CTML, meshing the verbal and pictorial representations with each other and with what is already known (Mayer, 2001). This prior knowledge is gained during our careers too. Different occupations will likely affect integration patterns and how these integrations are made will likely affect their comprehension scores.

In order to use these variables and this quantitative approach, some important assumptions were made. One theoretical assumption was that the healthy clinical participants would acquire the information from the ICF by using two channels (audibly

and visually) when given the audio/visual presentation and only through one channel with the standard method (visually/reading). The theory assumes that the participants will better absorb the information when presented with more than one channel of information. The CTML is based on three main assumptions: people have auditory and visual channels for processing information; there are limits to the channel's capacity; and filtering, selecting, organizing, and integrating information are all active learning processes (Mayer, 2001).

A topical assumption that was made was that the informed consent was not well understood or comprehended. Also, the informed consent form and process is required in all clinical research and the form must meet the requirements of the FDA (in the United States) and the federal guidelines. Ethically, this document should be designed so the person reading it can accurately understand what they are reading in order to be informed enough to volunteer their participation. According to CFR Section 26.116, "The information that is given to the participant or the representative shall be in language understandable to the participant or the representative. No informed consent, whether oral or written, may include any exculpatory language" (Office of Federal Register, 2013). The topic of IC comprehension assumes improvement of these inefficiencies is needed, but these improvements may not always work for all people.

Some methodological assumptions of quantitative research included (a) random assignment to experimental groups equalized participants across demographic variables, (b) use of quantitative standardized surveys supported objectivity, (c) use of statistical analysis, and was hypothesis-based. These assumptions helped control bias by quantitatively evaluating the comprehension of the two groups and comparing them

through SPSS to prove or disprove the initially proposed hypotheses. Positivists strive for sound scientific methods, in which the research is controlled and unbiased (Ponterotto, 2005). The researcher had no influence over the data collection and the results were intended to be generalizable to the population.

Sample

The population of interest was potential healthy subjects of clinical research. The sample included men and women between the ages of 18 and 55 with no known major health issues. The use of these participants helped to remove any evident confounding factors, and was viewed as an ideal group in which to begin examination of standard comprehension expectations. The target sample was 116 participants that met the above requirements in age and health. The acquisition of this sample was through a convenience criterion sampling. Inclusion criteria also included access to a computer with speakers that can play video files since it will be an online survey with an audio/visual presentation. Exclusion of participants was limited to those that did not identify English as their first and primary language.

Recruitment was initially done using an inactive database held by Covance, called *CoRA,* for potential Phase I non-oncology research trials. This database came from all subjects that had previously participated in any Covance Phase I study without issue, had not participated in the last three years, or were from closed Covance Research Units. There were over 50,000 healthy subjects in the system across the U.S. and near the Leeds, United Kingdom site. The administrator provided an export from the database of all of the email addresses of the people that fell between 18 and 55 years of age. Survey questions were included immediately following the IC to participate to evaluate the

remaining inclusion and exclusion criteria to help eliminate those that did not qualify. Although full names were not required to be provided, participants were allowed to fill out their name and address to receive compensation for their effort. There was also a potential that the names would be evident from the email addresses. However, full confidentiality was respected. Email addresses were held in a password-protected excel sheet and within the Fluid Survey system that is also password-protected. All information from the research will be held on a password-protected flash drive as well for seven years. The email blast was sent out to all participants' email addresses provided. Half of the approximately 3,200 recipients received a link to the paper ICF presentation and the other half received a link to the video ICF presentation. The email explained to them the reason for the survey and explained the survey was optional. There were also three additional email reminders sent to these participants over the course of the next three months (once-per-month reminders). The email did not mention Covance in any way, as requested by Covance to avoid any type of affiliation between this research project and Covance. This approach provided a convenience sample and access to all demographics of people that could participate in healthy participant research.

Due to a very low survey completion rate as well as very slow recruitment, three amendments to the original IRB application were made to the recruitment process in an attempt to improve the rate of recruitment. The first amendment to the original IRB application was to implement a dissertation-only Facebook page, rather than recruiting directly from the researcher's personal Facebook page. The Facebook page gave direct access to the Fluid Survey link. The link took them either to the paper ICF presentation or the video ICF presentation. This was randomly assigned. The dissertation page was

available to the entire Facebook database (publicly shared) and all people that viewed the page could share a link to it on their own page, as well. While this did increase the number of completed responses, the incoming data were still too slow. A second amendment to the original IRB application was submitted to utilize a survey company, Survata. This company took the video ICF survey and provided the survey directly to their large database of participants and they recruited for completed surveys. During this time, the link to the survey was unavailable through Facebook. The survey had such a low rate of completion that the company declined to post the survey after a week and a half. As a result, the only route of recruitment returned to the Facebook dissertation page.

Finally, the compensation was increased and a final amendment to the original IRB application was approved to provide every participant with a gift card and two flyers were approved for use. The compensation was increased to a 10 dollar gift card for every completed survey if the participant provided their address. The remaining participants were recruited using this method. In order to obtain 58 responses to each survey, for a total of 116 completed surveys, many surveys were started, but not completed. The entire recruitment period took 1 year. Of the 176 paper ICF surveys that were started, only 58 of these were completed, resulting in a survey completion rate of only 33%. The actual completion rate of the video ICF survey cannot be calculated exactly, as it cannot be determined how many individuals Survata had to reach out to in order to obtain its 21 completed surveys that were provided to the researcher. However, of the remaining 37 needed complete responses, 112 surveys were started for an estimated completion rate of 33% as well.

Each form of recruitment required different permissions and rules to follow in regard to recruitment and access. For the initial recruitment method, Covance *CoRA* administrator and the Covance legal group provided permission to receive the email list from the database and send the survey out to the participants' emails. For the second recruitment method, Facebook did not have to provide permission, and Survata followed its own standard operating procedures for recruiting for the third recruitment method that was used. These sites did not have their own IRB. The potential participants either received an email explaining that this study was for a dissertation research project and what the survey was about or read the same information prior to clicking the link to the survey provided on the Facebook page or when contacted by Survata. The informed consent at the beginning of the survey also relayed this information; all three routes of recruitment led to the IC being read prior to starting the ICF presentation and survey. The participant could take the survey anywhere they could access a computer that played video and audio. There will be no contact after the study and this was shared with the participants in the IC.

The following formula was used for calculating the sample size for a study using regression analysis like this one. The formula is $50 + 8 (k)$ with k being the number of independent variables being analyzed (Tabachnick & Fidell, 2006). There was one independent variable (predicted verbal IQ) being considered and two experimental groups. Therefore, for a sufficient data sample the study needed to evaluate 116 completed surveys.

Instrumentation

The instrument chosen to evaluate comprehension was The Deaconess Informed Consent Comprehension Test (DICCT) by Miller, Barbarash, Searight, Grable, Schwartz, and Sowell (1994) to assess the subject's comprehension of the informed consent. The original author provided permission for the use of the test utilized it in this study. The DICCT standardizes the assessment of informed consent comprehension (Miller et al., 1994). The DICCT was tested by correlating the instrument with two psychometrically established measures to see if it validly demonstrated subjects' comprehension of the informed consent (Miller et al., 1994). The test showed high validity and reliability in demonstrating IC comprehension. The DICCT was tested using healthy and educated subjects (275 of them) rather than geriatric and ill subjects, which the author found to provide inconsistent data (Miller et al., 1994). "Studies have increased numerically during the past decade, but investigation in this area has been hindered by methodologic and conceptual issues," (Miller et al., 1994, p. 877).

The DICCT is a 14-question open-ended survey with questions that relate to the eight basic sections of the IC (Miller et al., 1994). The questions are written at an eighth-grade reading level and in layman's terms. The subjects could earn up to 28 points for the survey (*0 = incorrect or no answer, 1 = correct, but incomplete, 2 = correct & complete*) (Miller et al., 1994). A mean score of 21.94 $\pm$ 3.17 would equate to good comprehension (Miller et al., 1994). The score calculated from the DICCT was integrated with the demographic information using the predicted verbal IQ equation.

Demographic questions were asked of all participants to allow for the calculation of the predicted verbal IQ. Predicted verbal IQ =

87.24 - (5.08 x occupation) + (1.77 x years of education) + (.17 x age).

Because this survey has been validated and found to be reliable there was no need to conduct a pilot or field test. The information gathered from the DICCT provided the researcher with what was needed to conduct the analysis. Additionally, the only other data that were collected was demographic data and this did not need to be tested either. Analysis was then performed to find out if the hypothesis was supported.

Data Collection

Initially, the participant either received a link to the online survey (Fluidsurvey.com) provided in an email along or by clicking on the survey link through the Facebook page, following an amendment to the original IRB application for recruitment. Data collection started when the participant consented to participate at the very beginning of the survey link. The inclusion and exclusion criteria were then presented in question form. If the participant did answer the age or computer requirement questions within the parameters of the inclusion and exclusion criteria, then they were not be able to continue on to the IC presentation or survey and were exited from the survey, thanking them for their time. Additionally, if they did not consent to participate, the survey closed and they were not able to move forward with the presentation or survey. If they met all of the inclusion and exclusion criteria, they moved onto their ICF presentation.

Following consent, the participant was offered either a standard paper ICF (control group) to read themselves, or an audio/visual presentation of the same ICF

(experimental group). Half of the participants received the standard ICF (58 subjects) and half watched the audio/visual presentation of the ICF. The participant had to have access to a computer with speakers that could play video files since was an online survey and could potentially have had an audio/visual presentation. Group assignment was done randomly for all participants by sending emails with differing survey links and by posting two different survey links at random. When one survey was answered more often than the other, the link to the survey that was less frequently answered was posted again and the other was deactivated. Participants were not able to return to the video or written ICF once they moved onto the survey. Once participants completed the presentation, the participants were asked their demographics including age, education level, occupation, residence, and gender. Following these questions, the DICCT was given. The 14 open-ended questions were answered and finally all information was submitted. These questions were then scored based on 0, 1, or 2. The answer was scored at zero for an incorrect answer, one for a correct but incomplete answer, and two for a correct and complete answer.

Each survey was scored by hand by the researcher. Inter-rater reliability was done by having another scorer independently score all of the survey responses as well. A 20% overlap of data was used to evaluate the Kappa coefficient between the two readers. Previous literature varies greatly on what percent is considered enough. Previous research demonstrated an acceptable overlap as low as 2% (Dale, Strickland, Symanzik, Franblau, & Evanoff, 2008), one at 10 % (Taplin & Reid, 1973), two at 20% (Carey, Morgan & Oxtoby, 1996; Joyce, 2013), and many that did not indicate a percentage (Chung, Chiang, Chou, Chu, & Chang, 2010; Riley, Holman & Fletcher, 2014). When

the Kappa score dropped below a level of 0.80, the two scorers met and discussed the scoring discrepancy, thereby maintaining a minimum of a 0.80 Kappa score; this occurred while reviewing the video consent results only. The resulting scores of DICCT were then compiled. The demographic data were then inserted into the predicted verbal IQ equation: 87.24 - (5.08 x occupation) + (1.77 x years of education) + (.17 x age). These data were then used in data analysis.

Data Analysis

SPSS software was used to analyze the data collected from the DICCT and the demographics. The comprehension level (DICCT scores) were analyzed comparing the standard ICF participants to the audio/visual presentation participants. The questions listed in Table 2 were answered using the software. The data were managed and analyzed within SPSS while the data were organized within Excel. Data were stored on a password-protected computer as well as backed up on a password-protected flash drive. The data will be maintained and stored for 7 years in case the data can be used in future work.

Table 2

Research Questions and the Statistical Methods Used to Answer Them

Research Questions	Statistical Method
What are the demographic characteristics of the study sample?	Appropriate descriptive statistics were used to describe the sample.
Do the experimental groups significantly vary by demographics (age, gender, occupation, residence, and education level)?	Differences in age by experimental groups were tested using an independent samples *t*-test. Differences in gender, occupation, and residence by experimental groups were tested using chi-square analysis. Differences in education level by experimental groups were tested using Mann Whitney U non-parametric test.
Does level of comprehension vary significantly by experimental group status (Group 1 standard consent form, Group 2 multimedia presentation)?	Differences in level of comprehension by experimental groups were tested using independent samples *t*-test.
Does level of comprehension of the informed consent vary significantly by predicted verbal IQ?	Differences in predicted verbal IQ were tested using regression analysis.
Does level of comprehension of the informed consent vary significantly by experimental group status after controlling for predicted verbal IQ?	Analysis of covariance was used to test group differences in comprehension level after adding predicted verbal IQ as a covariate.

Ethical Considerations

The study attempted to minimize ethical concerns by keeping the participants' full names anonymous (unless offered up by the participant to obtain a gift card), providing informed consent, and using a non-vulnerable sample. Confidentiality of the resulting data was not an issue since the survey was completed anonymously over the internet. The results of the information were not shared with the participant so there will be little concern regarding emotional distress. One ethical consideration is beneficence. Since the participant did not gain anything from this experience there was no benefit to them specifically. There was an explanation provided to the participant that the results will

ideally lead to better IC processes for the greater comprehension by participants in the future.

This study is considered to only be minimal risk. The information was collected from anonymous participants and involved an ICF for a mock study. The study did not examine a vulnerable population since only healthy participants were used. Participants were protected since their confidentiality was maintained and their participation was based on their willingness to participate through informed consent and completing the survey. Since Covance provided a list of email addresses, there was a possibility that some emails could identify a potential person in some way. To avoid breaches of confidentiality, the researcher maintained the email list on a password-protected Excel document and flash drive. Additionally the emails were sent directly from a password-protected survey site so there was no ability to leave the email in a sent box. Additionally, all email addresses will be permanently deleted after 7 years. None of the data collected from the Facebook page link to an email address or any other identifying information. The name and address provided by subjects to obtain the gift card was manually separated from their survey responses.

CHAPTER 4. RESULTS

Introduction

This quantitative, experimental study utilized a nonprobability, convenience sampling design to evaluate the comprehension differences between a standard ICF presentation (control group) and the audio/visual presentation of the ICF (experimental group). The CTML supports the hypothesis that the audio/visual presentation of the ICF would result in higher DICCT scores when holding predicted verbal IQ constant. The chapter will first describe the overall sample demographics and how they affect the assumptions that can be made about the results. Next, the results found during data analysis will be described in detail, and the impact the data have on the dissertation goals will be discussed. Additionally this chapter will re-examine the research questions and hypotheses defined in Chapter 1 and how the data did or did not support rejecting the null hypotheses. Finally, a summary will be provided to incorporate all of the findings of ICF comprehension in healthy subjects when comparing standard ICF presentation to a multimedia presentation of the same information.

Research Question 1

R_1: Do the sample demographic characteristics vary between the control and experimental groups?

a. What are the demographic characteristics of the study sample?

b. Do the experimental groups significantly vary by demographics (age, gender, occupation, residence, and education level)?

The sample of subjects contained some demographic characteristics that were diverse with large ranges, while others were unevenly represented. Participant age ranged from 18 to 62 years of age, with an average age just under 38. There was also a wide range of verbal IQ scores across both the control and experimental groups. In contrast, the participants were primarily female (84.5%), highly educated (92.2% had more than a high school degree), had high occupation scores (81.9% in the top two categories), and were urban-based (75.9%). One of the most important findings was the DICCT score. The score ranged from 2 to 26 out of a possible 28 points, with an average score of 15.07. A mean score of 21.94 $\pm$ 3.17 would equate to good comprehension (Miller et al., 1994). These scores (low and high) were across both groups and amongst highly educated people with all occupation scores. This demonstrates a lack of comprehension of the consent form across both groups. Table 3 summarizes some of the means of the demographics collected through the survey. Table 4 summarizes the means of the demographics by experimental group.

Table 3

Study Sample Demographic Characteristic Means

Variable	Minimum	Maximum	Mean[a]	SD
Age	18	62	37.62	10.03
Years of Education	12	16	14.89	1.56
Occupation Score	1	5	1.88	1.37
Predicted verbal IQ	86.32	121.20	110.62	8.99
DICCT Score	2	26	15.07	5.26

[a]Means are based on 116 participants.

Table 4

Group Demographic Characteristic Means

Group		Age	Years of Education	Occupation Score	Predicted verbal IQ	DICCT Score
1	Mean[a]	37.59	15.12	1.72	111.82	15.47
	SD	8.60	1.42	1.27	8.04	4.94
2	Mean[a]	37.66	14.66	2.03	109.43	14.67
	SD	11.37	1.64	1.46	9.78	5.59

[a]Means are based on 58 participants.

Descriptive frequencies of the data showed very interesting results. The first statistical test performed was an independent samples *t*-test on age across both groups. This was done to ensure that assignment to groups was actually random and there were no differences between the groups. On average, participants in the control group were 37.59 years old (SE = 1.129), while participants in the experimental group were 37.66 years old (SE = 1.493). This difference, -.069, 95% CI [-3.776, 3.638] was not significant t (114) = -.037, p = .971.

Next, differences in gender, residence, and occupation by experimental groups were tested using chi-square analysis. No statistical differences were found between experimental groups for gender, residence or occupation ($p \geq .05$). The findings of the chi-square analyses can be found in Table 5.

Table 5

Chi-square Analyses of Gender, Residence and Occupation by Experimental Groups

Variable	χ^2	*df*	*p*
Gender	4.209	1	.071
Residence	3.013	1	.083
Occupation	2.6491	2	.266

The difference in education level between the groups was tested using the Mann Whitney U non-parametric test. These tests were also used to evaluate if these

demographic characteristics played a factor in the predicted verbal IQ that could affect their DICCT score. Previously cited literature suggests that gender differences could affect verbal IQ, urban people have higher verbal IQ scores, and those with a more professional occupation or higher education also have higher verbal IQ scores (Jackson & Rushton, 2006; Crawford & Allan, 1997; Ritchie et al., 2013). Years of education did not differ significantly between the control and experimental groups (*Mdn* = 16 for both groups), U = 1438, z = -1.611, p = .107, ES = -.15. There were no statistical differences found between the control and experimental groups in any of these demographic characteristics. Consequently, none of these factors could confound the findings.

Two data collection issues regarding participant demographics should be noted. Participants were required to be between 18 and 55 years old. There were two instances within the survey for this to be confirmed. One participant answered the first question to confirm age eligibility correctly (if they had not, they would have been exited from the survey), but appears to have put in 62 when asked their exact age during the survey. The first question was asked prior to reviewing the ICF and required a yes or no answer while the second question came after the ICF and was answered in a free-text field. This person's age of 62 was included in the data as their real age cannot be confirmed. The second issue is regarding years of education. While it is evident that the sample had a minimum of a high school diploma, anything above 16 years (a college degree) cannot be ascertained from the data collected. The question asked the participant to provide their response to categories of years of education: 0-7 years, 8 years, 9-11 years, 12 years, 13-15 years, or 16 or more years. A change in how the information was analyzed makes it so there is no way to know how many years above 16 were completed and if the

participant completed 13, 14, or 15 years. Consequently, for this sample, participants were designated as 12, 13 or 16 years completed. This may have negatively impacted the predicted verbal IQ and the descriptive demographics on education for those in the two highest categories.

To evaluate the first research question (R_1), several analyses were performed. First, descriptive statistics (frequencies and means comparisons) were performed with the entire sample. Next, differences in age by experimental groups were tested using an independent samples *t*-test. Differences in gender, residence, and occupation by experimental groups were tested using chi-square analysis. Finally, differences in education level by experimental groups were tested using the Mann Whitney U non-parametric test. These data were analyzed to make sure that the groups were the same and how these demographics relate to the participant's comprehension of the ICF.

Research Question 2

$R_{2:}$ Does the level of comprehension vary significantly between the control and experimental groups?

The analysis performed to evaluate the second research question was an independent samples *t*-test on the DICCT score between the control and experimental groups. On average, participants in the control group (standard ICF presentation) scored 15.47 (SE = .648), while participants in the experimental group (multimedia ICF presentation) scored 14.67 (SE = .734). This difference, .793, 95% CI [-1.146, 2.732] was not significant t (114) = .810, p = .419. This demonstrated a slightly lower average DICCT score in the experimental group, however it was insignificant. The differences

between the groups were compared, and an independent samples *t*-test was performed on the DICCT score. This statistic was the basis of the more complex research questions.

Research Question 3

R_3: Does level of comprehension of the informed consent vary significantly by predicted verbal IQ?

To evaluate the third research question, a simple linear regression was calculated to predict DICCT score based on predicted verbal IQ score. A significant regression equation was found [F (1, 114) = 10.991, p = .001], with an R^2 of .088. Participants' predicted DICCT scores is equal to -4.132 + .174 (predicted verbal IQ). These results are slightly conflicting. The data do show that there was a positive correlation between predicted verbal IQ and DICCT scores. As predicted verbal IQ scores went up, so did the participants' DICCT scores. However, the model used only shows 8.8% (8.0% adjusted) of this prediction is based on predicted verbal IQ scores. There are other variables affecting DICCT scores that are not accounted for in this study.

A simple linear regression was performed to evaluate the relationship between comprehension (DICCT score) and predicted verbal IQ. The purpose of this analysis was to investigate if there was a relationship (negative or positive) between these two variables. The predicted verbal IQ score predicted the participant's DICCT score.

Research Question 4

R_4: Does level of comprehension of the informed consent vary significantly by experimental group status after controlling for predicted verbal IQ?

For the final analysis, a one-way ANCOVA was conducted to determine a statistically significant difference of ICF presentation type (group assignment) on DICCT scores when controlling for predicted verbal IQ scores. There was no significant effect of ICF presentation type on DICCT scores after controlling for predicted verbal IQ, F (2, 1) = 10.365, p = .686. These findings were not surprising for multiple reasons. As mentioned in the linear regression analysis, predicted verbal IQ was not a significant predictor of DICCT score. In order to accurately evaluate the effect of the experimental design between the two groups, the predicted verbal IQ was used as a control variable to eliminate the influence of verbal fluency. Removing predicted verbal IQ as an influence on comprehension allows for comparison of DICCT scores between the two groups and the presentation style of the ICF

Details of Analysis

The sample population was gathered from several different venues and was a convenience sample. Initial surveys were filled out by people included in the Covance database of previous Phase I (healthy volunteer) clinical research participants. Following the first recruitment amendment to the original IRB application, the population sample came from anyone that could access a dissertation page on Facebook. After the second amendment to the original IRB application, the Survata team reached out to their own sample population across the United States through their own advertising and recruitment means. Finally, after the last amendment to the original IRB application, participants were recruited from the Facebook page, email advertisement, as well as local flyer advertisement. The last two amendments to the original IRB application provided

participants with guaranteed compensation. Previous compensation was a chance at winning one of five gift cards.

Analysis was performed using IBM SPSS Statistics software version 22. Prior to the data being imported into the software, many steps were taken to ensure accuracy and to condense the raw data into the data needed for analysis. First, the responses to the 14 questions of the DICCT were read by the researcher and a second reviewer to grade each answer for a score of 0, 1, or 2 points. The second reviewer chosen has over 15 years of clinical research experience and conducts a second review of regulatory documents daily for work. These scores were then compared for inter-scorer reliability using the Kappa coefficient calculation for 20% of the data. Once all scores met the requirement of at least 0.80 then these scores were added to provide one DICCT score for each participant.

Next, the demographic data for education level (years of education), age, and occupation score were inserted into the predicted verbal IQ equation:
87.24 - (5.08 x occupation) + (1.77 x years of education) + (.17 x age) and each participant's predicted verbal IQ was then calculated. An average verbal IQ score is 100 with a SD = 15 (Wechsler, 1997). Some data had to be coded prior to being imported. Gender was coded 1 for male and 2 for female. This allowed for the SPSS software to read the variable as a recognizable nominal variable. Likewise, residence was coded 1 for rural and 2 for urban. These numbers were chosen and applied by the researcher; they were not pre-determined by the predicted verbal IQ. The occupation score was coded 1 through 5, and education levels were coded 1 through 6. These codes were predetermined by the predicted verbal IQ equation by Crawford and Allan (1997). Double data entry was then used to ensure accurate data entry on all data that would be

imported into SPSS. Original data were exported directly from the Fluid survey site into Excel. This data were then read and re-entered into a second and third Excel document. For the variables that required coding, the data were actually coded manually and then double data entered to confirm accuracy. All three of these Excel documents were then pasted into Word documents and the Compare option was used to evaluate any differences between them. Any necessary changes were made and the Compare function was run again until the documents were identical. Finally, one of the double entry files was imported into SPSS. Table 4 describes the coding that was used for occupation scores and education level.

Table 6

Coding for Education Level and Occupation Scores

Code	Education Level	Occupation Score
1	0-7 years (did not complete elementary school)	Professional
2	8 years (completed elementary school)	Intermediate
3	9-11 years (some high school)	Skilled
4	12 years (high school graduate)	Semi-skilled
5	13-15 years (some college)	Unskilled/ Not working
6	$\geq$16 (college graduate)	N/A

Summary

For the first research question, the researcher was unable to reject the null hypothesis. As defined by the statistical analysis above, the control and experimental groups did not significantly vary by any of the demographics evaluated. For the second research question, there was no significant difference found between groups for the DICCT score (ICF comprehension). Therefore, the null hypothesis must be retained. For

this research question, the researcher was able to reject the null hypothesis. While the data do show that the predicted verbal IQ was a significant (p = .001) positive predictor of DICCT score, it should be noted that there are other variables affecting DICCT scores that cannot be accounted for in this study. The H_1 was supported by the data, but further research needs to be conducted to better understand this relationship. Finally, for the fourth research question, the researcher was unable to reject the null hypothesis. Even after controlling for the predicted verbal IQ, comprehension was not significantly different between the two presentation groups. Additionally, the data showed no statistical difference between groups for the DICCT scores, education level, age, and occupation scores. These demographic variables made up the predicted verbal IQ score. These results indicate low comprehension of the ICF, regardless of education, age, residence, occupation, gender, predicted verbal IQ or ICF presentation style.

Overall, the sample was mostly female, highly educated, with high occupation scores, and lived primarily in urban residences. The DICCT scores were low across both groups and did not differ between groups. Despite having demographic descriptions that calculate into high predicted verbal IQs, average DICCT scores remained low, well-below the score considered for good comprehension. Although the data did show a significant positive relationship between predicted verbal IQ and DICCT scores, the data did not support the hypothesis that the multimedia presentation of the ICF would show higher comprehension levels after predicted verbal IQ was used as a control variable. Further research is necessary to understand multimedia ICF presentation styles effects comprehension.

CHAPTER 5. DISCUSSION, IMPLICATIONS, RECOMMENDATIONS

Introduction

The purpose of this study was to gain a better understanding of healthy subject comprehension of the ICF through the use of a multimedia presentation of the information. It has been demonstrated in ill patients that IC information presented in forms other than paper (i.e., multimedia or Power Point) can be helpful (Palmer et al., 2008). However, there is limited information available on whether or not these enhancements improve comprehension in healthy participants. This study used an online survey to evaluate comprehension of participants after either reading a standard ICF for a Phase I clinical research study or by receiving the same information via multimedia presentation. The DICCT was used to evaluate comprehension because of its validity and reliability and its applicability to this dissertation. Demographic questions were asked for two purposes, to understand the characteristics of the sample and to be able to calculate each participant's predicted verbal IQ score.

Mayer's Cognitive Theory of Multimedia Learning (CTML) provided the theoretical framework of the dissertation. The CTML suggests that people learn better when receiving information in two forms, or channels, rather the one (Mayer, 2001). The theory states that the brain does not incorporate the information in a multimedia presentation as a standalone learning experience. It pulls all of the words, pictures, and auditory information in and combines it with past experiences (Mayer, 2001). This theory guided the dissertation, as well as the research questions and alternative hypotheses that were presented. The goal of the study was to test whether those receiving the multimedia presentation of the ICF would have higher comprehension scores on

average than those receiving the standard ICF when controlling for other factors. Unfortunately, the data did not support this alternative hypothesis.

Discussion of Results

The results showed trends in the participants' demographics and possible study design flaws. Statistics on the sample demographics showed that the sample was primarily female (84.5%), lived in urban areas (75.9%), had a minimum of a high school degree, most had college experience (92.2%), and were approximately 38 years old. The null hypothesis that was retained for the first research question removed concerns over whether or not the sample was random. The sample was not, however, representative of the population it was pulled from. In both groups, average comprehension (DICCT) scores were below the range given for good comprehension (Miller et al., 1994). Although it was found that as predicted verbal IQ went up, the DICCT score also went up ($p = .001$), predicted verbal IQ was not a strong predictor ($R^2 = .088$). While the sample that participated was highly educated, had above-average verbal IQ, and had highly professional careers (81.9% in the top two categories), the DICCT scores were below-average for both experimental groups. Despite not supporting the alternate hypothesis, these results are supportive of the need for an improvement in informed consent comprehension. Even with the advantages the participants had (higher education and professional careers), their comprehension of the mock ICF was much lower than what is expected to show good comprehension.

As mentioned above, the only supported alternative hypothesis was that higher predicted verbal IQs would positively predict higher DICCT scores. Although this was found to be true in this sample, there were many other factors that could affect DICCT

scores that could not be accounted for from these data. The results did not show DICCT scores to be higher in the experimental group (multimedia ICF presentation). The analysis showed that there were no between-groups differences amongst any of the demographic characteristics. Because there were no confounding differences between the two experimental groups, demographic characteristics could not be the cause of the DICCT score not differing between the groups. For example, if one of the groups had a significantly higher predicted verbal IQ, then further exploration would be needed to identify why the DICCT score did not differ between the groups as would be expected. Furthermore, the alternative hypothesis, DICCT scores would be higher for the experimental group after the predicted verbal IQ was controlled for, was not supported by the data. The null hypothesis had to be retained that both experimental groups would have similar comprehension.

Overall, the results of the study did not support the Cognitive Theory of Multimedia Learning (CTML). The multimedia presentation of the ICF did not improve the comprehension of the participants in this sample. Despite these findings, the CTML still holds validity and should not be considered the reason the participants did not show improved comprehension. The theory has been supported many times previously and there were several studies discussed that did show that multimedia learning does promote improvement in ICF comprehension.

Discussion of the Conclusions

There are several conclusions that can be drawn from the data and the results of the analyses performed in this study. The data are greatly skewed by the demographics of the participants. There is no representation of many groups of people; those that

participate in Phase I studies tend to be less educated, a more equal gender representation, and often-times unemployed. A previous study found the average gender ratio to be 47.5% to 52.5%, male to female (Almeida et al., 2008). The same study also found the average age to be approximately 10 years younger than this study sample (26.4 years old) (Almeida et al., 2008). Additionally the findings showed 61.1% of Phase I participants are unemployed and almost 64% had only a high school diploma (Almeida et al., 2008). The surveys were answered by a very different group than this, and thus are unlikely to be able to be extrapolated upon to demonstrate the real-world participants' responses to the same survey.

It can also be concluded from the results that the DICCT score was not affected by the presentation style. Despite all of the factors that should increase DICCT scores (demographics utilized in the calculation of the predicted verbal IQ) based on previously cited literature there was a significant lack of comprehension of the ICF with both presentation styles. Previous research has shown a strong association with those with lower IQs before education and their later-in-life IQ scores (Ritchie, Bates, Der, Starr & Deary, 2013). Additionally, research has shown that IQ is a strong predictor of reading comprehension, but the data found in this study did not support this (Tiu, Thompson, & Luis, 2003). It is clear that other variables were affecting the DICCT scores and improved comprehension that was expected.

The CTML is based on three main assumptions: people have auditory and visual channels for processing information; there are limits to the channel's capacity; and filtering, selecting, organizing, and integrating information are all active learning processes (Mayer, 2001). The learner participates in active processing, attending to the

information that is coming in, organizing it into proper mental representations, and incorporating it into their current knowledge (Mayer, 2009). The CTML assumed that the multimedia presentation would increase comprehension of the ICF. The theory also assumed that those with previous life experiences and higher education should be better-able to incorporate the new information with previous information, and this would increase comprehension. Consequently, DICCT scores were expected to be higher in the experimental group when receiving the information from the ICF by watching and hearing a video explaining the information rather than just through reading a paper version. However, the data and analysis did not support these theoretical assumptions.

One factor that should be noted is that a large number of the participants taking the survey in the experimental group completed it prior to the amount of time it would take just to watch the video from start to finish (approximately 43%). This means that they did not complete the video prior to answering the questions. For those taking the paper survey, it was expected that reading the entire ICF would take approximately the same amount of the time as the video, 34 minutes. Of the completed paper survey responses, 81% of the participants completed the ICF reading and the survey questions within 30 minutes. This also supports an assumption that most responders did not read the entire ICF either. This likely greatly affected the DICCT scores of the respondents and the data were then unable to accurately demonstrate comprehension of the ICF.

Moving forward the goal is to consider the conclusions found both in studies that do support multimedia presentations of the ICF (or other enhancements) and those that do not support these enhancements to further our understanding of ICF comprehension. It is important to gather the information from research that evaluates the effects of

enhancements of ICFs and how these findings can improve clinical research practice. While the data did not support the multimedia presentation of the ICF in this study, general ideas for practice have been identified, limitations that can be addressed going forward have been considered, and ideas for future research have been compiled.

Implications for Practice

At this time, there are very few implications for practice from what was found in this research study. One major implication is that staff who are consenting healthy volunteers for Phase I studies should be aware that it is unlikely the potential participants comprehend the ICF during their time spent reviewing it in the clinic. Therefore, they should allow any tools (i.e. shorter ICFs, multimedia presentations, interactive quizzes) that can increase comprehension, give extra time for questions, allow participants to take the ICF home to re-review it, or use any other tool that will increase their understanding. It is important to note that clinical research personnel cannot assume participants fully understand the ICF. One last implication for practice is that because studies are not clearly defining the best way to gain informed consent from a research participant, clinical research staff should expect more research to be done. When the right method or methods are found that increase consent form comprehension it should be implemented.

Limitations

There were numerous limitations to this study. There were several limitations to note in the data collection design. By performing the ICF presentations online and allowing the survey to be answered anywhere, there was no control over the participants' surroundings, distractions, or time and effort put into answering the survey. This variable

differs from previous research in which the study was performed in a research clinic setting (Armstrong et al., 2010; Palmer et al., 2008; Paris et al., 2010). Participants could potentially be distracted by other people, other web pages, or a possible lack of interest in the survey. While only using online data collection removed any person as a potential participant that does not have direct access to a stable computer and internet connection, this likely had a minimal effect on recruitment since most people (74.4% of Americans) now have at-home access to the internet (U.S. Department of Commerce, 2014). Similarly, those without access to a computer with speakers posed little affect as currently 83.8% of Americans have access to one in their homes (U.S. Department of Commerce, 2014).

Another limitation was the length of the video and paper ICF. Both were lengthy and it is likely people could not remember it all by the end. Since they were unable to go back and re-review the presentation in order to answer the questions, this may have reduced the number of correct answers. In a real clinic setting, participants have the consent form in front of them and could continue to consult the ICF throughout the study if they do participate. The length of the video may have driven away participants and lowered the completion rate (Rowbotham et al., 2013). This is evidenced by the number of surveys that were not completed (approximately 68% of the incomplete surveys) after the first three questions were completed and prior to the ICF presentation.

A third limitation to the study was the use of the Covance inactive database for the majority of subject selection at first. The only way for a participant to be in the database is that they completed at least one clinical research Phase I trial previously, were active at previously closed Covance Clinical Research Units, or had not actively

participated in a Covance study in the last three years. Although the database had over 50,000 subjects in it to obtain participants from, not all subjects had email addresses and several of the emails were no longer accurate. The use of the database also meant that no one without prior clinical research experience could participate. If the database had remained the only method of recruitment, it would have also affected the generalizability of the findings. Participants naïve to clinical research would not have represented any of the comprehension data. By incorporating the Facebook page, naïve subjects had the opportunity to participate.

Limiting the study to only include participants whose first language is English could be considered a weakness. By not including this population, the generalizability of the results will be limited. However, if this study included non-native English speakers, it would introduce an additional variable that is beyond the scope of this study. This limitation will need to be addressed in a future study that focuses specifically on differences in comprehension for non-native English speakers.

Most of these limitations were all noted from the beginning, but may not have been as fully understood as to their effect on the overall study success. The biggest limitation seems to have been the length of the ICF and the apparent lack of people completing the ICF before completing the survey. This limitation not only was misjudged as minor prior to starting the study, but may provide bigger insight into the overall issue with ICF comprehension. Because of these limitations and the lack of statistically significant findings, further research is recommended.

Recommendations for Further Research

There are several recommendations for further research that have come from the completion of this study. Recommendations for future research provided below come both from the lack of findings in this study and from the limitations found during the course of the research. Future research is clearly needed to help identify the improvements needed to increase subject comprehension of ICFs. It is important to continue efforts in this topic, particularly in healthy subjects, a topic in which little research has been done previously.

One recommendation would be to conduct the research within the confines of a clinic setting. This would reduce distractions, represent a more real-life clinical research scenario, and provide an opportunity for all people that fit the other inclusion and exclusion criteria to participate. It would not require a person to have their own internet connection or computer with speakers and video capabilities. For people with transportation issues, there are always taxi vouchers, public transportation options, and other ways to get people into a clinic. It would not be feasible to provide participants with a computer or internet connection in their home. This setting would also provide the participant with the opportunity to ask questions, much like they are able to do during a real study, and concentrate solely on the ICF presentation, either standard or multimedia.

Another recommendation would be to compare the two presentation styles again, but limit the length of the video and/or the paper ICF. Comprehension may increase if researchers are able to portray the same ICF information in the video, but in a shorter amount of time. At a minimum, it should improve compliance with completing the ICF prior to answering the survey questions. Additionally, unlike the current design, it may

be more beneficial to allow the participant to access either presentation style throughout the survey questions for reference and to be more representative of a Phase I clinical research study.

Recruitment for the research could be improved in future efforts as well. Utilization of a database of potential participants that consists of older information was not ideal. One suggestion for future recruitment would be through university postings or classrooms (appealing to a younger participant group). Reaching out to facilities in which lower-income and less-educated people are more prevalent would also allow for a more generalizable population sample. Finally, recruitment through other clinical research studies (conducted as a sub-study) could also be an option.

Future research is also needed in not-native English participants, an area that has little exploration at this time. The efforts involved with this would be much greater than what could be accomplished in this dissertation. Research both in comprehension in English ICFs and in native language-translated documents and videos could be completed to understand if the information is better comprehended in native language. Previous research actually showed that an ICF comprehension was better in English in HIV-positive participants in Botswana than their native Setswana (Chaisson et al., 2011). However, this is the only study found to consider this, leaving another gap in the knowledgebase.

Additional research is needed to evaluate how the multimedia ICF presentation could be improved, overall. It would be helpful to determine what aspects of the video increased participant comprehension. Specifically, determining factors such as if video clips of procedures were more beneficial than static pictures of the items used in those

procedures would be helpful for future video development. Surveys could also be given to assess satisfaction with each presentation style. Furthermore, surveys could ask for feedback on parts of the video to determine which aspects are most easily-understood. Other multimedia presentations of the ICF could also be considered and evaluated in this same way.

Future research could also be conducted using participants to complete the survey after both presentation styles. One way to improve validity and decrease outside variables would be to hold each participant as his or her own control. By having the same participant view both ICF styles and answer the same survey they can reduce confounding factors. However, this method would require a large amount of time to pass between the two tests as repeating the same information could, in itself, improve comprehension as proven by previous literature. Finally, future research should be performed on a much more diverse group of participants to help generalizability of the findings. One way to obtain a more diverse group would be to conduct the study in several areas of the United States, including areas in which there are lower-income families, those without a college education, those in rural residences, or those with less professional careers. Including those demographics that are similar to those that actually do participate in Phase I clinical research studies is important to the validity of the findings.

Conclusion

There has been a lot of research done to investigate comprehension of ICFs in clinical research. Incorporation of audio/visual information into the presentation improves consent form comprehension in vulnerable populations (Palmer, Lanouette, &

Jeste, 2012). Most of the research has been conducted in ill patients, rather than healthy subjects. Additionally, the research that has been conducted to find other options to increase comprehension scores has not been able to provide a clear determinate of what works best (Paris et al, 2010; Paris et al., 2007; Stunkel et al., 2011). This study sought to fill a gap in the knowledgebase.

The researcher looked to test if a multimedia presentation of the ICF increased comprehension scores in healthy Phase I clinical research subjects. However, the participants that completed the survey did not end up representing the healthy Phase I clinical research population. Results demonstrated that in this particular study, there was no increase in DICCT score in the experimental group that received the multimedia ICF presentation. Furthermore, the study did clearly demonstrate that despite having a highly educated, professional, participant pool with above-average IQ scores, comprehension of the ICF in either format resulted in poor comprehension with a low mean DICCT score in both groups (15.47 in the control group and 14.67 in the experimental group).

Although numerous null hypotheses were unable to be rejected, there was a great deal of information gleaned from this study. Recruitment of the study was slow and arduous due to several design flaws, participants were not representative of the population, and despite several factors that improve comprehension for the participants, the comprehension of both ICF styles was poor. These findings all lead the researcher to conclude that ICF comprehension is still an issue that needs addressing and that more research is necessary. There were outside factors that affected the lower DICCT scores and it is necessary to conduct future research to explore these issues; there were also several limitations identified with this study. Furthermore, there may be some variables

that may not be controllable in any research study. However, it is the researcher's responsibility to continue efforts in improving ICF comprehension as much as possible to provide subject safety and truly informed consent for participation in clinical research.

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APPENDIX A. MOCK INFORMED CONSENT FORM

INFORMED CONSENT AUTHORIZATION TO PARTICIPATE IN A RESEARCH STUDY

Title: (Protocol #: CAP2014) A PHASE I RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF SINGLE AND MULTIPLE DOSES OF CAPELLA2014 IN HEALTHY ADULT VOLUNTEERS

Principal Investigator: (Main Study Doctor)	**John Smith, MD**
Site of Research Study:	MacArthur Clinical Research Unit, Inc. 123 Highway 51 Alien, NV 99999
Telephone #:	(555) 544-1234
24 hour Telephone #:	(800) 235-6543
Sponsor:	Capella Students Inc.

You are invited to participate in a research study. However, before you give your consent to be a research participant, we want you to read the following and ask as many questions as necessary to be sure that you understand what your participation will involve.

MacArthur Clinical Research Unit, Inc. is paid to test new drugs. The study doctors in this study work for MacArthur, but do not have a financial interest in the outcome of this study.

NATURE AND PURPOSE OF THE STUDY
An investigational drug is a drug or a form of a drug that is not approved by the U.S. Food and Drug Administration.

CAPELLA2014 is an investigational drug that is being developed as a therapy used to prevent cytomegalovirus (CMV) infection in the developing fetus of women who obtain the virus during pregnancy. CMV belongs to the herpes virus family and is a common virus that infects many people at some time during their lives but rarely causes obvious illness except when your immune system is severely weakened or the infection occurs during pregnancy. CAPELLA2014 is designed to block infection of CMV into human cells.

The purpose of this study is to evaluate the safety and tolerability of single and multiple doses of the study drug and to measure how much of the drug gets into the blood stream and how long it takes the body to get rid of it when taken by mouth by healthy volunteers.

This is the first time that this study drug is being given to humans.

This study is for research purposes only and is not intended to treat any medical condition. Information about any side effects that may occur will also be collected.

RESEARCH PARTICIPANT SELECTION
You have been invited to participate in this research study because you are a healthy male or female subject between 18 to 55 years of age. Research participants for this study must meet certain requirements.

Females must not be pregnant or nursing, and either post-menopausal (defined as interruption of regular menstrual periods for at least 2 years or if less than 2 years must be confirmed with a blood hormone test), surgically sterile (e.g., hysterectomy or removal of ovaries) or must agree to use an acceptable method of contraception from Screening until 113 days after the last dose of study drug. Males must be sterile or agree to use an acceptable method of contraception from Screening until 113 days after the last dose of study drug. The acceptable methods of contraception are listed in the "Birth Control Requirements" section of this document.

It is important that you answer all of the screening questions completely. You must disclose all past and present diseases, allergies and all medications that you are taking, including prescription and non-prescription drugs.

Approximately 672 research participants will be enrolled in this multi-site research study. Approximately 116 subjects will be enrolled in a single ascending dose group; approximately 218 subjects will be enrolled in a multiple ascending dose group; approximately 338 subjects will be enrolled in a multiple dose expansion group. **This consent form is for the Single Ascending Dose Group.**

STUDY DURATION
The duration of your participation in this study is approximately 86 days, not including the screening visit. This study requires 1 research unit confinement of 3 days/2 nights followed by 5 outpatient visits and 1 follow up outpatient visit. A screening visit is required within 28 days prior to the start of the study.

STUDY DESIGN
This study is considered a dose escalation study. This means that the first group of research participants will be randomly (by chance) assigned to receive the lowest dose of the study drug or placebo. Placebo is an inactive study drug, "dummy oral capsule." At the first dose level 4 research participants will receive the study drug and 2 will receive placebo (i.e., you have a 2 out of 3 chance of receiving the active study drug). If after evaluation of the study findings for the first group, it is determined that no serious side effects occurred that require that the study be stopped, a different group of research participants will be enrolled and the next higher dose level will be given. In all of the subsequent groups, 4 research participants will receive the study drug and 1 will receive placebo (i.e., you have a 4 out of 5 chance of receiving the active study drug). The same process will be followed before enrolling research participants in each dose level. The study can be stopped at any time based on the effects of the study drug.

The dose levels planned for this study are 1 mg/kg, 3 mg/kg, 5 mg/kg, and 10 mg/kg (2 mg/kg, 6 mg/kg, 10 mg/kg, and 20 mg/kg total).

You will not have a choice as to which dose level you are assigned nor will you have a choice as to the placebo or study drug assignment.

Neither you nor the study doctor will know whether you are receiving study drug or placebo. However, this information can be made available if medically necessary.

Study drug will be given on Day 1.

Screening
You will come to the research unit for a screening visit to determine if you are eligible and willing to participate in this study. Prior to any procedures being performed, you will be asked to sign this informed consent form. During this screening visit, a medical history, review of your demographics (sex, age, ethnicity and race), measurement of vital signs (temperature, pulse, blood pressure, respiration rate), height, weight, ECGs (heart rhythm tracing), and review of inclusion and exclusion criteria will be performed. Blood and urine samples for clinical laboratory testing will be obtained. A screening for HIV, hepatitis, and drugs of abuse will be done. If you are female, a pregnancy test will also be performed. Postmenopausal women may have a blood hormone test performed.

Human Immunodeficiency Virus (HIV) is the virus that can cause Acquired Immunodeficiency Syndrome (AIDS). Before you can qualify to be in this study, you must test negative for HIV antibodies. Antibodies are substances produced by the body's immune system to fight infection. A blood test can show if you have been exposed to, or are infected with HIV. Agreeing to have the HIV test done is a voluntary decision that only you can make. However, if you choose not to have the HIV test performed, you will not be able to participate in this study. The HIV antibody test will be done confidentially. A positive HIV result does not mean that you have HIV or AIDS and a negative test result does not mean that you are not infected because it can take up to three months for the test to indicate infection. Positive results for hepatitis and HIV must be reported to a local health agency. This is the legal obligation of health professionals in this state. Depending on sponsor requirements, you may be asked to sign a separate HIV consent form for some studies. If you are disqualified for study participation by other screening procedures or if you do not complete the screening visit, it is possible that this testing will not be completed.

You will be permitted to participate in the study at the discretion of the study doctor if the results of the study screening laboratory tests and other assessments are satisfactory. Screening procedures may need to be repeated in order to qualify for this study. You will be advised of the study restrictions and when to report to the research unit to begin the study. You may be considered an alternate for this study until such time that you have received study drug.

MacArthur checks in more people than are needed for the study in case someone fails to check-in or becomes ineligible for the study. Not everyone will be chosen to stay in the study long enough to take the research drug/product.

Some screening procedures may require repeating at check-in to confirm eligibility. These tests may show a change from Screening that indicates a change to your health or physical being which may make you ineligible at check-in**.**

If you are not chosen to stay in the study, you will go home from the research unit the same day or the next morning. You will be paid for the time spent in the research unit.

STUDY PROCEDURES

Periodically during the study your vital signs will be measured and ECGs may be performed, you will be asked about how you are feeling and if you have taken any drugs. In addition, the blood and/or urine samples collected in this study will be used for routine clinical laboratory testing and study drug analysis.

Please note that the exact schedule for the procedures described in this consent form is subject to change. Some procedures may not be performed, and some may be added or moved to other study days.

Day -1 (Admission Day)
You will report to the research center the day prior to dosing, Day-1 to begin your first clinic confinement. Blood and urine will be collected including testing for drugs of abuse and a pregnancy test for women. A test for alcohol via a breathalyzer will be performed. You will have a physical examination and triplicate ECGs (taken 3 times in a row) performed. Your medical history will be updated. Your weight and vitals will be measured.

Day 1
You will have a blood sample collected prior to dosing which includes testing for CMV infection and antibody. A physical exam, triplicate ECG, and measurement of your weight will be performed. You will receive your dose of study drug. Following dosing you will have blood samples taken 2 times over the next 4–6 hours. A triplicate ECG will be performed within 1 hour post dosing.

Day 2 (Discharge Day)
You will have 1 blood sample taken. A physical exam and a triplicate ECG will be performed and you will be permitted to leave the clinic. At the completion of the clinic confinement you will be given instructions and told when to return for the outpatient visits.

Days 4, 8, 15, 29 and 57 (Outpatient Visits)
You will come to the research unit on each of these days for an outpatient visit. A blood sample will be collected including antibody testing on Days 29 and 57 only. A urine sample will be collected on Days 8 and 29. A physical exam will be performed. A triplicate ECG will be performed on Day 8 only.

Day 85 (Follow-up Visit)
You will come to the research clinic for your last outpatient visit. A blood and urine sample will be collected. A test for CMV infection and antibody will be performed. A physical exam, triplicate ECGs, and measurement of vital signs and weight will be performed. All females will have a pregnancy test performed. At the end of these study procedures your participation in the study will be complete.

If you should develop a visible side effect, such as a skin rash, you may be asked to allow pictures of the side effect (rash) to be taken for the study records.

If necessary, the study doctor may require that you stay longer for observation in the research unit or for additional laboratory testing based on the effects of the study drug or the results of the laboratory tests.

Meals

Standardized meals and snacks will be served at regular times during your research unit confinements except when fasting is required or otherwise noted.

Blood Sampling

Blood samples will be taken approximately 12 times throughout the course of the study. Approximately 223 mL of blood, (about 3/4 cup), will be drawn throughout the study. Additional blood samples may be required if any of your laboratory tests are abnormal. It is possible that more than one attempt to obtain a blood sample may be necessary.

For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 2 cups of blood. Additional blood samples may be drawn during the study if the study doctor considers it necessary for monitoring your health.

An IV catheter (a small flexible tube) may be inserted into a vein (by a needle) in your arm and kept open in order to collect blood samples. The catheter will be checked, maintained, and may be changed if necessary.

Withdrawal Procedures

If you withdraw early from the study, for any reason, you will be asked to complete the laboratory testing and end of study procedures outlined in the "Day 85" section listed above.

RESTRICTIONS

You may not consume any alcoholic beverages within 12 hours prior to study Day -1 and 12 hours prior to each outpatient visit. You must limit your consumption of alcohol to less than 2 units per day (1 drink is 12 oz of beer, 5 oz of wine, 1.5 oz of spirits, or equivalent) during confinement at the research unit as well as after discharge from the clinic and for the remaining study visits.

You may not use any prescription medications/products (excluding oral, implantable, and injectable contraceptives and hormone replacement therapy) within 7 days prior to dosing and throughout the duration of the study unless considered acceptable by the study doctor.

You may not use any over-the-counter drugs and non-prescription medications (including vitamins, minerals, and phytotherapuetic/herbal/plant-derived preparations) within 7 days prior to Check-in and throughout the duration of the study.

You must not use any concomitant therapy with agents other than acetaminophen; non-steroidal anti-inflammatory drugs (NSAIDs); oral, injectable, or implantable contraceptives; and hormone-replacement therapy, unless acceptable by the study doctor or deemed necessary in a medical emergency.

You must not use any vaccines (including seasonal flu and H1N1 vaccines) within 7 days prior to the Screening Visit.

You must refrain from strenuous activities or exercise from 48 hours prior to Check-in and during the clinic confinement and will otherwise maintain your normal level of physical activity.

You must not smoke more than 10 cigarettes a day from the Screening Visit and until study completion.

Male subjects must agree not to donate sperm from Screening until 113 days after the last dose of study drug.

Research Participant Responsibilities
As a research participant you will be asked to complete the study procedures for this study, come to the research unit for all of your scheduled visits, follow the instructions listed in this informed consent form, and notify the study doctor if any information regarding your health or availability to participate in this study changes.

RISKS AND DISCOMFORTS
This research study is the first time that the study drug is being tested in humans.

CAPELLA2014 is an antibody that targets a common virus called CMV. The antibody does not target any human proteins but only targets the virus. Approximately 50% of the US adult population has been infected with CMV. Once you are infected with CMV, you are infected for life, but the infection is latent (not measurable). Generally, CMV does not cause symptomatic disease and is not measurable in people who have a normal immune system. Thus, there is no anticipated benefit or risk to you if you have been infected with CMV.

CAPELLA2014 have been tested in animals in multiple doses of up to 200 mg/kg in rats. CAPELLA2014 did not reveal any toxicities that were due to administration of the study drug. The meaning of these findings in humans is not known.
This is the first study that CAPELLA2014 has been studied in humans. Because this is a monoclonal antibody that has not been evaluated in humans previously, there is a risk of having an allergic reaction. The most frequent adverse events reported with the administration of monoclonal antibodies are those related to ingestion reactions, especially with the first dose. The most common signs and symptoms reported are fever, chills, shortness of breath, chest tightness, skin rash, high or low blood pressure, wheezing (bronchospasm), headache, low oxygen level in the blood, hives and swelling of the face, throat, mouth and tongue. Treatment with antibodies can potentially result in a life-threatening allergic reaction called anaphylaxis, but this is rare. You will be monitored by medical staff during and after dosing to detect and promptly treat any symptoms if they occur.

<u>Study Procedure Risks</u>
During the collection of blood samples, you may experience pain and/or bruising at the needle injection site/catheter. Although rare, localized clot formation and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw/catheter insertion.

ECG patches may cause a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement of ECG leads.

UNKNOWN/UNFORESEEABLE RISKS
In addition to the risks listed above, there may be some unknown or infrequent and unforeseeable risks associated with the use of this study drug, including allergic reaction or interaction with another medication.

You will be informed in a timely manner both verbally and in writing of any new information, findings or changes to the way the research will be performed that might influence your willingness to continue your participation in this study.

RISKS TO THE UNBORN

Pregnancy/Fetal Risks: The effects of the study drug on the unborn are unknown **and may be hazardous.**

If you think that you have become pregnant during the study it is important that you inform the study doctor immediately. If you become pregnant or think that you may be pregnant, you may be removed from the study and the study doctor will refer you to seek obstetric care, the cost of which will be your responsibility. The study doctor may request to track your pregnancy and will report the pregnancy and outcome to the Sponsor and the Investigational Review Board (IRB).

BIRTH CONTROL REQUIREMENTS

Females of childbearing potential must agree to use an acceptable method of contraception from Screening until 113 days after the last dose of study drug. The acceptable methods of contraception are as follows; IUD with spermicide; female condom with spermicide; contraceptive sponge with spermicide; diaphragm with spermicide; tubal ligation/occlusion with a second acceptable birth control method; permanent contraception (including Essure®); oral contraceptives, implants, injectables; hormone replacement therapy that have had stable doses for at least 3 months along with another method and a male sexual partner who agrees to use a male condom with spermicide.

Males must be sterile or agree to use an acceptable method of contraception (e.g., male condom with spermicide); a female sexual partner must not be pregnant or lactating and must be postmenopausal or surgically sterile (as described in the "Research Participant Selection" section of this document), or must agree to use an acceptable method of contraception (e.g., IUD with spermicide; female condom with spermicide; contraceptive sponge with spermicide; diaphragm with spermicide; tubal ligation/occlusion with a second acceptable birth control method; permanent contraception [including Essure®]; oral contraceptives, implants, injectables, and hormone replacement therapy that have had stable doses for at least 3 months along with another method) from Screening until 113 days after the last dose of study drug.

BENEFITS

Participation in this study is purely for research purposes, and will not improve your health or treat any medical problem you may have.

You may benefit by having physical examinations. The results of laboratory tests done at the screening visit will be made available to you upon request. However, if you are disqualified for study participation by other screening procedures, some laboratory tests may not be conducted.

COST

There is no cost for participating in this research study (the study sponsor pays all the study costs); however, you are responsible for any transportation and/or living costs incurred while traveling to and from the research unit. This includes having adequate travel arrangements should you not be selected for the study for any reason.

PAYMENT FOR BEING IN THE STUDY

You will be paid for taking part in this research study as outlined below. This is to compensate you for your time and inconvenience. Each portion of the research study has a dollar value assigned to it, which accumulates as you participate in this study.

Payment Schedule

Screening Visit	-0-
Research unit Confinement Nights (2 nights x $400.00)	$800.00
Outpatient Visits –(6 visits x $250.00)	$1,500.00
Follow-up Visit	$395.00
TOTAL	$2,695.00

Total compensation for study completion will be $2,695.00. If you choose to withdraw from the research study, you will receive payment only for the portion of the study that you have completed as outlined above. If it is necessary for you to return to the research unit for additional safety follow up visits, you will be paid $150.00 for each completed visit.

If you are selected as an alternate and not selected to participate in the study you will be paid $250.00 for each overnight stay. As an alternate, if you test positive for any unauthorized drugs or alcohol you will not be paid.

All research participants will be paid within 21 days of the completion of their participation in the study.

In agreeing to participate in this study, you will be acting in your individual capacity, not as an employee of MacArthur Clinical Research Unit, Inc. No taxes are deducted from your check. You are responsible for paying any state, federal, or Social Security taxes. You will be required to provide your Social Security number or tax identification number to MacArthur, if you have one. If you receive more than $600 in one calendar year from MacArthur, you will receive a 1099 tax form the following January. MacArthur reports the money paid to you to the Internal Revenue Service.

If you do not have a social security number or tax identification number, the Internal Revenue Service (IRS) requires MacArthur to deduct 30% from your compensation. You will need to follow IRS guidelines to determine if you are eligible for a refund or contact a certified tax accountant to assist you.

ALTERNATIVE TO BEING IN THIS STUDY
Since this study is not intended to provide any therapeutic or other health-related benefit, your alternative is to not participate in this study.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY
You are free to withdraw from this study at any time, and you agree to inform the study doctor immediately if you intend to withdraw for any reason. To end your participation in this study, you must contact the study doctor at the contact information listed on page one of this informed consent form. You may be asked to come to the research unit or doctor's office to complete some end of study procedures which are listed in the Withdrawal Procedures section of this document. Your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of benefits to which you are otherwise entitled.
The study doctor in charge of the research study can remove you from this study without your consent for any reason, including, but not limited to:

a. His/her judgment that any condition or circumstance may jeopardize your welfare such as increased risk, change in potential benefit, or the integrity of the study.
b. Your failure to follow the instructions of the study staff.
c. If the study is stopped by the sponsor, study doctor, or FDA.

It is possible that because of the effects of the study drug, the study doctor may determine that it is unsafe for you to drive a motor vehicle. If you wish to leave the study, the study staff will make the necessary arrangements for you to leave safely.

OFFER TO ANSWER ANY QUESTIONS ABOUT THIS STUDY
If you have any questions, concerns, or complaints during screening or during this study, or if you think you may have experienced a research-related injury, you should contact Dr. John Smith at (555) 544-1234 or (800) 235-6543.

If you have any questions regarding your rights as a research participant, please contact the On-your-Side Investigational Review Board, Inc. at toll free (888) 888-8888 from 9:00 am – 5:00 pm (Eastern Time), Monday–Friday. You can also contact the On-your-Side Investigational Review Board, Inc. if you would like to report problems in a research study, express concerns, ask questions, request information, or provide input. The On-your-Side Investigational Review Board is a committee established for the purpose of protecting the rights of participants in a research study. For more information about your rights and role as a research participant you can visit the Research Participant section of the On-your-side Investigational Review Board, Inc. website at www.oysirb.com.

CONFIDENTIALITY/MEDICAL RECORDS
Your medical information will be kept as confidential as possible within the limits of the law. However, absolute confidentiality cannot be guaranteed. Your medical information may be given out if required by law. If information from this study is published in a medical journal or presented at scientific meetings, you will not be identified by name, picture, or any other personally identifying information.

The following people and groups of people may look at and/or copy your medical records to make sure that the study is being done properly and to check the quality of the data:

- Capella Students, Inc. study monitors and representatives
- Capella Students, Inc. collaborators and licensees (people who partner with Capella Students, Inc.)
- The Institutional Review Board responsible for protecting the rights and safety of the subjects who take part in research studies
- The FDA and other government agencies involved in keeping research safe for people

If you sign this document, you give permission to MacArthur Inc. to use or disclose (share) your health information that identifies you only for the purposes of this research study and for research directly related to the use of CAPELLA2014 in disease therapy and diagnosis.
The health information that you are giving permission to be used and shared includes all health information about you that has been and will be created or received by MacArthur Inc. and that is in your medical record kept by MacArthur Inc.

This health information about you may be used by and/or disclosed (shared) to representatives of the FDA, other health and regulatory authorities, the Institutional Review Board, Capella

Students, Inc., and Capella Students, Inc.'s representatives, study monitors, collaborators, and licensees (people and companies partnering with Capella Students, Inc.).

Those persons who receive your health information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by laws that apply to them. Therefore, absolute confidentiality cannot be guaranteed.

You do not have to sign this consent form, but if you do not, you may not take part in this research study. You are free at any time to limit MacArthur Inc.'s use and sharing of your health information, without penalty or other consequence. However, you may not be allowed to take part, or continue to take part in this research study if at any time you choose to limit MacArthur Inc.'s use and sharing of your health information that is necessary for the completion of this research study.

You have the right to see and get a copy of your medical records kept by MacArthur Inc. that are related to the study. However, by signing this consent form you agree that you will not be able to review or receive some of your records related to the study until after the entire study has been completed.

You may change your mind and revoke (take back) this authorization at any time. If you revoke (take back) this authorization, no new health information will be collected about you. However, Capella Students Inc. will still be able to use and disclose any health information about you from this research study that has already been collected. To revoke (take back) this authorization, you must write to the study doctor listed on Page 1 of this form.

Your authorization (permission) to use and disclose (share) your health information will continue indefinitely, but that use and sharing will only be for the purposes described in this Informed Consent Form.

POSTING OF RESEARCH STUDY ON WEB
A description of this clinical study will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

BUSINESS CONFIDENTIALITY
The information and any materials or items that you are given about or during the study - such as information identifying the research unit, the Sponsor, any study drug(s), and/or the type of study being performed - should be considered confidential business information of MacArthur and the study Sponsor. You are of course free to discuss such information under confidence with your doctor or with your friends and family while considering whether to participate in this study or at any time when discussing your present or future healthcare. However, distributing confidential business information as described above to the media or posting it on the internet is prohibited.

STUDY DATA, INCLUDING BLOOD AND URINE SAMPLES
All specimens and samples obtained from you during this study will be used and kept for the purposes described in this Informed Consent Form, and all data and materials created during this study will be the property of Capella Students, Inc. Capella Students, Inc. has no plans to pay you or to share with you any potential profits that Capella Students, Inc. may receive from such specimens, samples, data or materials.

IN CASE OF INJURY
Your safety is the major concern of every member of the staff. Please contact the study staff as soon as possible if you have side effects or injuries. The phone number for MacArthur is (800) 666-9999 or (678) 910-1234.

MacArthur will provide immediate medical treatment and follow-up care, without cost to you, for side effects or injuries caused by being in this study. The costs for any other medical problems not caused by being in this study are your responsibility. Financial compensation for such things as lost wages, disability or discomfort due to injury is not available.

You **DO NOT** waive any of your legal rights by signing this form.

CLOSING STATEMENT
You have read the information which has been stated above and have received satisfactory answers to all of the questions which you have asked and you willingly sign this consent form. You will receive a copy of the signed informed consent document. You hereby consent to be a participant in this study.

You may withdraw this consent at any time.

SIGNATURES*:*
Please read the following paragraph out loud to the person obtaining the consent.
I have read the above information in a language that I understand well. The content and meaning of this information has been explained to me. **I have asked the staff any questions I may have and have had enough time to decide if I want to take part in this study.** I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information.

_____	_____
Print Participant Name	Participant Signature
_____	_____
Date	Time
_____	_____
Signature or Initials of Person conducting the Informed Consent discussion and verification of literacy	Date

I have received a copy of this study consent form.

_____

Your Signature Date

APPENDIX B. STATEMENT OF ORIGINAL WORK

Academic Honesty Policy

Capella University's Academic Honesty Policy (3.01.01) holds learners accountable for the integrity of work they submit, which includes but is not limited to discussion postings, assignments, comprehensive exams, and the dissertation or capstone project.

Established in the Policy are the expectations for original work, rationale for the policy, definition of terms that pertain to academic honesty and original work, and disciplinary consequences of academic dishonesty. Also stated in the Policy is the expectation that learners will follow APA rules for citing another person's ideas or works.

The following standards for original work and definition of *plagiarism* are discussed in the Policy:

> Learners are expected to be the sole authors of their work and to acknowledge the authorship of others' work through proper citation and reference. Use of another person's ideas, including another learner's, without proper reference or citation constitutes plagiarism and academic dishonesty and is prohibited conduct. (p. 1)
>
> Plagiarism is one example of academic dishonesty. Plagiarism is presenting someone else's ideas or work as your own. Plagiarism also includes copying verbatim or rephrasing ideas without properly acknowledging the source by author, date, and publication medium. (p. 2)

Capella University's Research Misconduct Policy (3.03.06) holds learners accountable for research integrity. What constitutes research misconduct is discussed in the Policy:

> Research misconduct includes but is not limited to falsification, fabrication, plagiarism, misappropriation, or other practices that seriously deviate from those that are commonly accepted within the academic community for proposing, conducting, or reviewing research, or in reporting research results. (p. 1)

Learners failing to abide by these policies are subject to consequences, including but not limited to dismissal or revocation of the degree.

Statement of Original Work and Signature

I have read, understood, and abided by Capella University's Academic Honesty Policy (3.01.01) and Research Misconduct Policy (3.03.06), including the Policy Statements, Rationale, and Definitions.

I attest that this dissertation or capstone project is my own work. Where I have used the ideas or words of others, I have paraphrased, summarized, or used direct quotes following the guidelines set forth in the APA *Publication Manual*.

Learner name and date: Amanda L. Beasley 14Mar2015

Mentor name: Andrea Daines, PhD