University of Alberta

Beyond Length:

Issues in the Study of Informed Consent

by

Rodney Michael Schmaltz 

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of requirements for the degree of Doctor of Philosophy

Department of Psychology

Edmonton, Alberta

Spring, 2007

Your file Votre référence
ISBN: 978-0-494-29737-7
Our file Notre référence
ISBN: 978-0-494-29737-7

Dedication

For my friend, mentor, and supervisor, Mike.

Abstract

The consent form is a controversial issue in human research. Researchers and participants complain of lengthy consent forms that discourage participation while failing to add further protection to the humans involved. The majority of the empirical work on the consent process indicates that increasing consent form length and providing additional information is associated with a lower rate of consent. The current study examines a potential confound in the previous research and investigates the real world impact of consent form length on rates of participation. In Experiment 1 (N= 56), participants compared two consent forms that contained similar information but varied in length. The findings indicated that consent form length alone had little impact on consent rates. In Experiment 2 (N=61), participants were asked to evaluate consent forms that varied only in their description of harms. Expanding the harms section of the consent form by adding dictionary definitions resulted in lower rates of consent. This finding can be explained by reference to the availability heuristic (Tversky & Kahneman, 1973) which suggests that when making judgments, people rely heavily on information that comes to mind most easily. In Experiment 3 (N=92), participants evaluated consent forms that were manipulated by expanding the harms section, as well as manipulating the risks involved in the study itself. Results indicated that expanding the harms section of a consent form with dictionary definitions lowers consent rates, but only in high risk studies. In Experiment 4 (N=140), participants were again asked to read consent forms that varied in detail of harm and potential risk but they were led to believe they had the opportunity to actually take part in

the study described. Again, expanded information about potential risks in participation was associated with lower rates of consent in high risk studies.

Acknowledgements

To fully describe the impact that Professor Mike Enzle has had on my personal and professional life would take volumes. From recommending research strategies to the brilliance of Robert B. Parker, Mike has always guided me in the best direction. I consider myself lucky to have had the opportunity to work with Mike, and more importantly, to know him as a friend. Thanks to my co-supervisor Dr. Cor Baerveldt. From patrolling Whyte Avenue to debating psychology, it's been an honour to work with Cor. Thanks to my supervisory and examining committee, Dr. Kim Noels, Dr. Jeff Schimel, Dr. Glenn Griener, and Dr. Paddi O'Hara. Your insightful comments have been greatly appreciated.

Graduate school (and life in general) would have been far less enjoyable without Martin, Trevor, Walter, Geoff and Brian. I have relied on fellow division champions Martin and Trevor to provide proper advice on whether to continue working, have a beer, or play basketball. You both possess sage like wisdom. I have appreciated Walter's tireless efforts to claim gold in the Guinness challenge. Maybe one day, Walter...keep up the good fight. From waking up in the wrong house to walking from St. Albert to Edmonton, Geoff and I have had many adventures over the years. I hope the people of Cincinnati are prepared for you. Brian is the only person I know who can fully appreciate the nuances and intricacies of Strapping Young Lad. Respect.

My parents, Jeannie and Harold, are my inspiration. Their love, support, good humour and encouragement mean the world to me. From preschool to graduate school, they have always been there for me.

Finally, the captain of stress patrol, my best friend, and the love of my life, Michelle. Your uncanny ability to make me laugh in times of maximum stress is hard to believe. I couldn't have done this without you. I love more than you will ever know (though I am going to spend the next eighty or ninety years trying to show you).

Table of Contents

LIST OF FIGURES

CHAPTER 1: GENERAL INTRODUCTION

Introduction

The consent form is a contentious issue among researchers and has garnered much empirical attention. In the biomedical sciences, criticism of the consent process has ranged from claims that consent forms fail to provide sufficient information for participants to make an informed decision (e.g., Byrne et al., 1988) to claims that the consent form itself actually increases risks to participants (Myers et al., 1987). Researchers agree that it is important for participants to have sufficient information to allow for a fully informed decision regarding consent (Holmes, Margetts & Gibbs, 1979), and there is an ongoing debate as to how best to achieve a truly informed consent procedure.

The provision of informed consent is a fundamental component in the major codes of ethics governing research with humans, such as the Nuremberg Code, Declaration of Helsinki, The Belmont Report, and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS). According to the Nuremberg Code, one of the earliest ethical guidelines for research on humans, the first basic moral principle that must be observed when conducting ethical research is that "the voluntary consent of the human participant is absolutely essential." This provision of voluntary consent serves the dual purpose of protecting participants' welfare and their autonomy to make an informed decision (Annas et al., 1977).

The TCPS (Article 2.1) states that:

Research governed by this Policy (see Article 1.1) may begin only if (1) prospective subjects, or authorized third parties, have been given the

opportunity to give free and informed consent about participation, and (2) their free and informed consent has been given and is maintained throughout their participation in the research.

While it is clear that consent should be considered a *process* and not just a document that is presented at the beginning of participation in a study, this is often not the case (Eyler & Jeste, 2006). As members of Research Ethics Boards become increasingly concerned about the need to divulge information to prospective research participants, the consent form grows longer and more complex. Also, as physicians and researchers are increasingly pressed for time, the standard procedure to gain consent is simply to provide the participant with a lengthy document to read and sign at the beginning of the study.[1] Researchers and participants increasingly view the consent form as a legal contract rather than a document to protect the autonomy of the participant. (Dawes, O'Keefe & Adcock, 1993).

Currently, the informed consent provisions in codes of ethics are built on anecdotal evidence and good intentions. Any evidence of the effectiveness of these provisions is generally negative evidence. If participants have not been harmed, then it is assumed that the codes must be working. In specific instances where participants' welfare or rights have been shown to be dramatically violated, changes have been made to ethical codes. (For instance, Milgram's (1964) infamous study of obedience led to specific limitations on the use of deception in human research (Baumrind, 1964)). The majority of research ethics codes are reactive (McDonald, 2000). The Nuremberg Code was introduced in reaction to

the atrocities committed by the Nazi doctors during the Second World War and other ethically troublesome research (Adair, 2001). Additional codes and alterations (e.g., American Psychological Association Code of Ethics, Canadian Psychological Association Code of Ethics, and more recently the TCPS) have been in response to unethical conduct that was not addressed by prior codes of ethics. The goal of the new codes or alterations to previously existing codes is to react to an ethical misstep, and then put assurances in place that this will not reoccur. Although there has been a wealth of research looking directly at human research ethics, much of the research has not been adopted into policy.

Issues in Research on Informed Consent

To change ethical guidelines based on idiosyncratic cases reflects good intentions and common sense. It does not, however, observe the normal scientific rules of evidence and generalizability that should guide decision making and policy making. One of the reasons that research on ethics does not appear to be informing policy makers is that the research tends to be inconsistent. For example, some research shows that providing information on the concept of randomization is associated with greater understanding of this concept, while other research indicates the opposite (Edwards et al., 1998).[2] Thus, over fifty years of research on the consent process has left us with conflicting evidence that is difficult to incorporate into actual participant protections. It is hypothesized that the inconsistency in the empirical evidence regarding the impact of the consent form on the overall consent process is due to two main factors: different

methodological approaches to the study of consent and the lack of distinction between consent for treatment and consent for participation in clinical research.

Methodological Issues in the Study of Informed Consent

One cause of the inconsistency in this research is due to the methodological problems involved in studying ethics. There are two main approaches to studying the consent form in clinical trials. One approach involves manipulation of the consent form for an actual trial, and the other is to have participants read hypothetical consent forms. While both approaches have value, they also present researchers with a difficult task to ensure that these results generalize to all clinical trials.

The problem of studying consent across these types of trials is that it is nearly impossible to standardize the procedure to control for confounding variables. Each clinical trial is unique, and the manipulation of the consent form is constrained by the parameters of that particular clinical trial (Joffe et al., 2001). For example, on the use of a new painkiller participants in a Phase II oncology trial may respond differently to a consent form than participants in a Phase III migraine study. Any differences found in the effectiveness of certain types of consent forms may likely be confounded with issues such as risk of participation, anxiety regarding the trial, health of participants, or age.

An illustration of this effect can be found in Simes et al. (1986) research on cancer patients who were randomly assigned either to receive a comprehensive overview of research which they could participate in, or to be given information at the discretion of the physician. Simes et al. found that the participants in the

comprehensive condition were more anxious and less likely to participate. These results indicate that increasing disclosure leads to lower rates of consent. This conclusion may be flawed for several reasons. One concern in this study is the generalizability of results. Does an increase in disclosure uniformly impact all clinical trials, or is there something unique about cancer research where more comprehensive disclosure leads to declining consent rates? One possible explanation for this effect is that the risks in cancer research are greater than those in other clinical trials. If this is the case, participants may be less likely to provide consent, as participation may involve harms or risks that most people are not willing to endure (e.g., nausea, loss of hair, etc.).

Even if the results did not generalize to other trials, this research could still be potentially valuable to participants in clinical trials regarding cancer if not for one major flaw. The manipulation is such that there is concern regarding experimenter bias. The physicians in this study knew which condition their participants were in, which may have influenced how they portrayed the information regarding the research. It is likely that physicians prefer to disclose information at their discretion, rather than provide patients with a comprehensive overview (M. Enzle, personal communication). If physicians feel more comfortable disclosing information at their own discretion, the physicians in this study may have been more likely to overemphasize risks in the comprehensive disclosure condition than in the discretion of physician condition. An overemphasis of risk by the physician, intentional or unintentional, in the comprehensive condition would seemingly provide evidence that the physician's

discretion is the best approach, when in fact, this finding may simply be due to experimenter bias.

Simes et al. (1986) research highlights only one potential problem when conducting research on consent within the context of an actual clinical trial. To help alleviate potential confounds, many of the studies conducted on the consent process use hypothetical consent forms in a laboratory setting (e.g., Gallo et al., 1995, Davis et al., 1990). By randomly assigning participants to different hypothetical consent forms, the researcher is better able to control for potential confounds such as experimenter bias. While this method of study has value, it is certainly a different experience for a participant to read about and consider a hypothetical study than to actually agree to participate in a clinical trial (Cassileth et al., 1980). Again, there is an issue of generalizability. For example, a patient who is undergoing a kidney transplant may feel additional pressure to consent as they may believe that a lack of participation could upset their doctor. This experience is significantly different from a first year psychology student entering a classroom with a group of other students to read and judge a hypothetical consent form. This is not to say that this type of research is not valuable, or that consent research on participants or undergraduates should not be continued, but rather that this difference should be noted when globally evaluating the research on consent.

Treatment versus Research.

In literature reviews or discussions of informed consent, consent for treatment (e.g., surgery) is often treated the same as consent for biomedical

research (e.g., Verheggen & Wijmen, 1996). Although there may be overlap when considering issues such as comprehension and readability, the distinction between treatment and research should be clear when studying rates of consent. If a patient is providing consent for the physician to conduct a surgery, the patient may not have any alternatives to surgery, or at least not perceive any alternatives to surgery. If this is the case, the importance of the consent form may diminish as the patient has already implicitly provided consent by seeking out treatment. A research situation is considerably different. If the participant decides not to participate in research, there is should not be any cost to their health, whereas the decision not to provide consent for surgery may be potentially fatal.

Rationale for the Present Study

The consent form has been the subject of numerous studies, so much so, that the study of informed consent has been called a grant-funded "cottage industry" (Slovenko, 1999). While there are the criticisms of further research on consent, the impact of the consent form on the overall consent process is a complex issue, and one that demands further research. Lavori et al. (1999) argue that "we should strive continuously to improve the effectiveness of methods for informing prospective research volunteers about experimental studies, thereby enhancing the protection of their interests." The purpose of this research is to investigate one important aspect, that of consent form length, with the goal of enhancing participant protections and providing recommendations for research ethics boards (REBs) and policy makers.

Researchers have previously investigated which factors most impact comprehension rates on consent forms (e.g., Stuart, 1978), the impact of different types of methods of administering consent (Tindall et al., 1994), competency of participants (Grossman & Summers, 1980), impact of educational levels on research participants (Faden, 1977) and how increasing the length of a consent form may impact participant consent rates (Epstein & Lasagna, 1969). The focus of this research will be to show that consent form length is a negligible variable in regards to consent rates, and to focus on how and why risk section manipulations impact consent rates.

Although there are many dimensions of the consent form that demand empirical attention, consent form length is of particular importance. As consent forms continue to expand (LoVerde, Prochazka, Byyny, 1989), researchers are concerned that a lengthy consent process is discouraging potential research participants to agree to consent. Researchers and physicians alike perceive the need for this increase in length due to the demands found in national and institutional codes of ethics, and not for reasons of enhanced participant protections (Ziker, 2003).

The literature on the impact of consent form length on consent rates, like much research on informed consent, is filled with inconsistencies. This research builds upon an oft-cited study that implies increased consent form length leads to decreased understanding of the information regarding the experimental trial and decreased consent rates (Epstein & Lasagna, 1969). Epstein and Lasagna's (1969) research was chosen as a reference point for several reasons, the most

critical being that the research is still often cited (e.g., Palmer, 2006; Patel et al., 2004) and it appears to be flawed. As well, Epstein and Lasagna's conclusions can be challenged by research in cognitive psychology that provides a strong alternative hypothesis for the findings.

In Epstein and Lasagna's (1969) research, the length of the consent form was manipulated by expanding the risk section. The goal of this research was to look at the effects of providing additional length; however, the consent form in the "short form" condition provides significantly different information than in the "long form" condition. For example, in the short form condition, participants are warned that "Fatal allergic reactions occur in rare instances, even with normal doses." and "Allergic reactions are more likely in asthma patients." In the "long form" condition, participants read that allergies:

> May take the form of skin rashes, or of swelling of the eyelids, tongue, lips, face and stomach and intestine; a red swelling of the entire face may occur. Hives may also be observed. If swelling occurs in the throat, the patient may not be able to breath. Many patients who react badly to this drug have a history of allergic disease, especially asthma, but sometimes allergic reactions occur in otherwise healthy people, even with small doses of the drug, and may rarely be fatal."

The long form condition has added risk of facial and intestinal swelling, hives and throat swelling. Epstein and Lasagna have also provided vivid descriptions of the risks, rather than simply expanding the risk section. They

conclude that increasing information leads to decreased understanding and amplified anxiety; however, this is not necessarily the case.

Understandably, participant anxiety was significantly higher in the long form condition. This increase in anxiety was likely due to the addition of risks, and not to a lack of comprehension due to increased length. The suggestion that understanding declined in the long form condition may be a methodological artifact. Patients were given a test on their knowledge of the information contained in the consent form. The consent form in the long condition was over four times longer than the form used in the short condition and contained significantly different information. The questions were identical for all participants and were structured such that "it was theoretically possible to get a perfect score after reading any of the three forms." If the questions were designed such that all participants could answer them, the additional information in the long form might hinder performance because the questions are focused on the information in the short form. The authors conclude that information presented to participants should be brief to maximize comprehension and intelligent decision making. The conclusion may indeed be correct, but Epstein and Lasagna's (1969) research is not designed to test this assertion.

Although Epstein and Lasagna's (1969) conclusions are generally well-accepted in the literature, there has been some research which indicates that consent form length does not necessarily lead to an increase in anxiety. For example, in a comparison of clinical consent forms versus research consent forms, Hopper et al. (1995) found that although clinical consent forms were 59% shorter

than research consent forms, they were harder to understand. Hopper's findings comparing clinical and research consent forms, while not the focus of this study, provide evidence that length alone does not necessarily impact understanding. Edwards et al. (1998) analysis of the literature on consent indicates that full disclosure of potential risks (e.g., adding additional possible risks) may result in better understanding, but still lead to an increase in anxiety (e.g., Simes et al, 1986). Other research has found that if people are presented with additional information anxiety does not increase (Lankton et al., 1977). Again, an inconsistency in the literature on consent is found; some research indicates that increasing information is associated with increased anxiety, while other research fails to show this effect.

In regards to the initial work conducted by Epstein and Lasagna (1969), it appears that the consent forms used in their research vary greatly in listed harms and not simply in length. That is, length is confounded by degree of potential harm. Another explanation for Epstein and Lasagna's findings may be found in previous research which indicates that people often rely on judgmental heuristics when assessing personal risk (Covello, 1983, in Stanley, Sieber & Melton, 1996). Cognitive psychologists have conducted a great deal of work on decision making, much of which can be applied to improving the consent process. Previous research on assessment of risk indicates that people often rely on judgmental heuristics when assessing personal risk (Covello, 1983, in Stanley, Sieber & Melton, 1996). These types of mental shortcuts generally allow people to make

judgments quickly and efficiently, but may lead to costs in accuracy (e.g., Nisbett & Ross, 1980; Gigerenzer & Goldstein, 1996).

One concept that may be particularly important to the consent form process is the availability heuristic. The availability heuristic suggests that when making judgments, people rely heavily on information that comes to mind most easily. For example, classic research on this phenomenon illustrate that when asked if more words begin with the letter K or have K as the third letter, most people incorrectly state that more words begin with the letter K. In fact, far more words have the letter K as the third letter. The reason people make this error is because it is easier to bring to mind words that begin with the letter K than have K as the third letter (Tversky & Kahneman, 1983). Slovic et al. (1983) demonstrated that people employ this type of heuristic processing when evaluating potential risks in research participation.

Slovic et al. (1980) propose that the availability heuristic is of importance in understanding how participants consider risk in the context of research participation. In Slovic et al.'s research, participants were presented with vivid descriptions of potential risk in research participation. Highly imaginable risks were associated with an increase in anxiety regarding research participation. Slovic et al. contend that participants were using the availability heuristic, and the most accessible information was the vivid descriptions to which they were previously exposed. This research partially explains the findings of Epstein and Lasagna's work. Epstein and Lasagna inadvertently manipulated vividness of risk with consent form length. Although Epstein and Lasagna tried to prevent

changing the meaning or impact of risk terms by adding information from a pharmacology textbook, the additional information is sufficiently vivid to allow for heuristic processing to impact decisions on consent.

The research of Slovic et al. (1980) provides further evidence that people employ the availability heuristic in decision making regarding risks but it is somewhat artificial with regard to the actual impact on consent rates. Consent forms used in clinical trials do not usually give vivid descriptions of potential risks; rather, the risks are typically listed or presented in point form. The availability heuristic likely impacts consent rates but not in the manner described by Slovic et al.

When participants read and consider risks in research they may rely on the most accessible example of when they have last encountered such a list of risk terms. Outside of research participation, there are only a few instances where people observe or consider a list of potential clinical risks, for example: when taking medication, and when appraising advertising for medication. In both of these cases, the information that is most accessible is associated with relatively low risk. In advertisements for medication, the focus is on the benefit of the medication while the risks, when mentioned, are an afterthought and often, and quite literally, tacked on to the end of the print or televised advertisement (e.g., see Appendix A). The listing of risks here is associated with an improvement in health, rather than the actual risk.

In terms of common medications such as cough suppressants or pain-killers, a list of risks is provided but the majority of people do not experience

severe adverse reactions. In the case of over-the-counter drugs, such as codeine, people report feeling tired or lightheaded but also report less pain. The risk term again is associated with a relatively positive outcome. Therefore, if people consider the risk terms in a consent form like they consider those found on medication, they will likely diminish the severity of the risk.

Overview of the Present Study

The purpose of this research was to investigate the impact of consent form length on consent rates without changing the potential risks involved in participation. Follow up studies tested the hypothesis that participants in research use the availability heuristic when assessing potential risks in research, and investigated what may be done to ensure that participants employ deeper processing when assessing potential risk.

As this research is built on the work of Epstein and Lasagna (1969), the initial experiments replicate their procedure of using a hypothetical consent form. In Experiments 1 through 3, participants are aware that they will not actually be participating in any research which they read about. Experiment 4 uses a behavioral measure and is meant to replicate the experience of a participant entering a Phase I trial. Participants in Experiment 4 were made to believe that they were actually going to be participating in the research which they read about.

Measures

The primary dependent measure is whether or not participants would provide consent to be involved in research described in varying consent forms. Additional exploratory measures were incorporated into Experiments 1 through 4

to investigate how consent form manipulation impacted how participants felt about the research, the consent form in general, and whether there was any effect on how they perceived the research itself.

Terminology

The experiments that follow describe research participants reading and responding to a variety of consent forms. To alleviate confusion, "participants" will refer to those who are actually involved in this research. "Subject" will refer to the person referenced in the hypothetical consent form stimuli.

Ethical Review

All research was approved by the University of Alberta Faculties of Arts, Science and Law Research Ethics Board. Experiments 1 through 3, participants were required to read and sign a consent form prior to the study. In Experiment 4, experimental demand concerns did not allow for informed consent prior to the beginning of the research. Participants in Experiment 4 were allowed to withdraw their data upon completion of the study. A full discussion of the ethical issues in Experiment 4 can be found in the methods section.

Language

The only data that were used in the analyses came from participants who had English as a first language, or those who had French as a first language with reported fluency in English. Gender was also recorded, although previous research indicates that gender does not affect willingness to participate in research (Patel et al., 2004).

CHAPTER 2: EXPERIMENT ONE

Introduction

The purpose of Experiment 1 was to clarify the work of Epstein and Lasagna (1969) by investigating the impact of consent form length on consent rates. Experiment 1 involved a comparison of consent forms that varied in length, but did not differ in risk. The goal of this research was to allow the results to be applied to a clinical setting, thus the manipulation needed to fall within the range of changes that actually take place in a biomedical trial. The consent form used in this study was based closely on a consent form previously used in a clinical trial. The wording remained similar, but the drug names were changed and based on published research.

Method

Participants and Design

Participants were 56 undergraduate university students who volunteered as part of an optional credit component towards an introductory psychology course for their participation. Participants were randomly assigned to a condition where they read a regular length consent form (standard condition) or a shortened version (short condition) of the same consent form. Experimenters were 9 senior undergraduate students.

Procedure

It was important that participants be allowed to read the consent form at their own pace and not feel pressured one way or another by the reading speed of another participant. Previous research indicates that the presence of others does not impact males rate of consent, however females were less likely to participate

in research when accompanied by someone else who also refused consent (Finney, 1984). For this reason, only one participant was involved in each experimental session. In addition, the consent form was similar to one used in a previous clinical trial. In many clinical trials, the participant is provided with the consent form individually and allowed time to read it alone.

The participant was greeted outside the lab by an experimenter and was asked to be seated. Once the participant was comfortable, the experimenter explained that the purpose of the study was to evaluate a consent form that had previously been used in a clinical study. The experimenter ensured that the participant understood that they would not be participating in the research that they were about to read in the experimental consent form, and that the purpose of the experiment was only to evaluate the consent form. The experimenter handed an envelope which contained the experimental stimuli to the participant, and then waited out of view until the participant finished. The stimuli in the envelopes were sorted randomly and the experimenters were blind to participant condition.

The participants in both conditions read the consent form for a study titled "A Multicentre, Double-Blind, Randomized, Flexible-Dose, Placebo-Controlled Study of Zolpidem in Patients with Major Insomnia". The consent form was adapted from a form used in a previously completed clinical trial. The information that was omitted from the standard form was information which would not alter the participants' ability to understand the study, nor hinder their ability to make an informed decision to partake in the research. The goal was to see if length alone impacted participant consent rates and participant perception of

the research. The impact of the information that was omitted was pilot tested among the research group (N=9). The experimenters were asked individually to compare the consent forms and assess whether there was any significant information that was found in one consent form, but not in the other. The consensus among the experimenters was that the information deleted did not significantly change the description of the research in the experimental consent form. See Appendix B for the short form and Appendix C for the long form.

Measures

Participant perceptions of the consent form were assessed using a series of scales based on previous research on the consent process (e.g., Chee Saw et al., 1994; Wagner, Davis, & Handelsman, 1998). Participants indicated on a 9-point Likert scale how they perceived various dimensions of the consent form. As mentioned earlier, the primary focus of this research was to investigate the impact of additional consent form information on participant rates of consent. The item of critical interest was "Would you participate in this research?" In addition to a self-report measure of willingness to participate, participants also responded to questions regarding how well the consent form was written (e.g., "Do you think the Consent Form was well done, well written?"), consent form length (e.g., "How much do you agree with the following statement, "The consent form was too long."?"), consent form understanding (e.g., "How much do you agree with the following statement, "I understood the consent form."?") and several questions on how the participants felt about the research described in the consent

form (e.g., "I believe the research project described in the consent form was valuable.").

Understanding of the information provided in the consent forms was measured through self-report. Previous research has used measures to test comprehension by interviews (e.g., Gallo et al., 1995) and structured questionnaires (e.g., White et al., 1984). The dimension of understanding being tested in this study was *perceived* participant understanding. If the participant reported that they fully understood the study, there was not a follow-up measure to ensure that this was true. This perceived measure of understanding was used as it most closely replicates the measure of participant understanding in a real clinical trial. For example, if a participant reads a consent form and is asked by the research coordinator if they understand, a simple yes is all that is required. For better or worse, it is unlikely that a participant is asked to recall aspects of a consent form before they begin a trial or demonstrate to the research coordinator that they accurately understand the experiment. A copy of the dependent measures can be found in Appendix D.

Results

A one-way analysis of variance (ANOVA) indicated that participants who read the short consent form were no more likely (M=5.04, SD=2.377) to agree to participate in the research than those who read the long consent form (M=5.07, SD=2.20), p=.959, ns. The difference in length did not impact the likelihood that participants would agree to partake in the research regardless of the length of the consent form.

The length of the consent form had no impact on the participants except for the unexpected finding for the item "I think that most people who are asked to be in this study will read the entire consent form carefully." Participants in the standard condition reported that it was more likely other participants would read the entire consent form ($\underline{M}$=8.04, $\underline{SD}$=1.26) than participants who read the short form ($\underline{M}$=6.69, $\underline{SD}$=2.78), $F(1, 54)=5.33$, $p \leq .03$. Although outside the scope of this research, future studies will be conducted to investigate this finding.

To ensure that the participants were not impacted by differing information, rather than simple consent form length, there were a number of questions addressing the quality of the information in the consent forms. There were no significant findings on the items "The consent form was poorly done"; "After reading the consent form, I would have questions for the researcher to answer before I would decide to participate in this study."; "Do you think the consent form was well done, well written?", "How clear would you say the consent form for the "Study of Zolpidem" research was?", "How well would you say the possible benefits of the study were described in the consent form?; and "How well would you say the possible harms were described in the consent form?" That there was no significant difference between these items individually, or as a cluster, indicates that the additional information in the long consent form was neither detracting from, nor adding to the informational content of the consent form. The results of Experiment 1 indicate that consent form length does not have a significant impact on the consent process.

CHAPTER 3: EXPERIMENT TWO

Introduction

The results of Experiment 1 provide evidence that increasing consent form length without adding significant risk does not increase anxiety or decrease consent rates. It did not, however, shed any light on the impact of understandability on the likelihood of obtaining participant consent.

Epstein and Lasagna (1969) hypothesize that increased understanding leads to an increase in consent rates although this is not necessarily supported by research looking at the grade level of consent forms. Goldstein et al. (1996) analyzed 284 consent forms used in biomedical research involving humans and found the average reading level (approximately 12^{th} grade) to be too high to be considered appropriate. Despite the assumed lack of understandability of these consent forms, they were approved by Institutional Review Boards and were being used to successfully recruit participants.

The purpose of Experiment 2, therefore, was to look at the impact of clarifying risk terms in a consent form on participation rates without affecting readability, vividness or length. Although it appears to the author that Epstein and Lasagna (1969) increased perceived risk by expanding the risk section of their experimental consent forms, it could be the case that the participants did not fully understand the meaning of the terms used in the short consent form condition of their research. If Epstein and Lasagna's hypothesis concerning understandability is correct, clarifying the terms listed in the risk section should lead to an increase in consent rates.

The experimental consent form used in Experiment 2 was similar to the form used in Experiment 1. The short form was not rated significantly different on understanding and quality; therefore, it was considered an appropriate choice for Experiment 2. To clarify risk terms, dictionary definitions were added to the risk terms in one condition.

Method

Participants and Design

Participants were 61 university students who received research credit toward an introductory psychology course requirement. Participants were randomly assigned either to a condition in which they read a consent form with a risk section expanded with dictionary definitions (expanded condition) or to a condition where they read a consent form with a risk section that only listed potential risks (standard condition). The consent form in the standard condition was written in a similar manner to the majority of consent forms used in clinical trials. The majority of consent forms used in clinical trials only list potential risks, and rarely expand on them.

Procedure

The procedure was identical to Experiment 1. In Experiment 1, consent form length was arbitrarily manipulated, and the risk section remained identical. In this study, the potential risks on the consent form in both conditions were the same, except that in the dictionary condition each risk listed was followed by a brief adapted dictionary definition. When adding the definition to each harm term, changes were only made so that the definition made sense in terms of the context

of a consent form. In the standard condition the risk section consisted of the following:

- daytime drowsiness
- dizziness
- lightheadedness
- constipation
- diarrhea
- dry mouth
- Although unlikely, this drug can cause memory loss
- A serious allergic reaction to this drug is unlikely, but could include:
    - rash
    - itching
    - swelling
    - trouble breathing

The risk section of the extended condition consisted of the following:

- daytime drowsiness – a persisting or lasting urge to sleep during the day
- dizziness - which may include having a whirling sensation in your head leading to a feeling that you may fall down
- lightheadedness – you may feel mentally disoriented
- constipation – most likely an abnormally delayed or infrequent bowel movement
- diarrhea – abnormally frequent bowel movements with more or less fluid stools

- dry mouth – not enough saliva, or spit, to keep your mouth wet
- Although unlikely, this drug can cause memory loss, including problems concentrating, and an inability to retain information
- A serious allergic reaction to this drug is unlikely, but could include:
    - rash - small marks on the skin
    - itching - a general irritation on your skin
    - swelling – for example, your ankles or fingers may expand beyond normal
    - trouble breathing – you may gasp for air and be unable to take deep breaths

The dependent measures were the same as those used as in Experiment 1.

Results

Manipulating the risk section of the consent form had an impact on the likelihood that participants would consent to the study. A oneway ANOVA indicated that the participants in the expanded condition were less likely to participate ($\underline{M}$=3.66, $\underline{SD}$=2.11) than did those who were in the regular condition ($\underline{M}$=5.41, $\underline{SD}$=2.18), $F(1, 59)=10.18$, $\underline{p} \leq .05$. There was a marginally significant difference on how free participants felt to consent. Participants felt less free to consent in the expanded condition ($\underline{M}$=7.38, $\underline{SD}$=2.09) than in the standard condition ($\underline{M}$=8.24, $\underline{SD}$=1.27), $F(1, 59)=3.77$, $p=.057$. Participants in the expanded condition felt that the study would be more unpleasant ($\underline{M}$=4.22, $\underline{SD}$=1.56) than participants in the standard condition ($\underline{M}$= 5.41, $\underline{SD}$=1.32), $F(1, 59)=10.30$, $p \leq .05$; more comfortable in the standard condition ($\underline{M}$=5.48,

SD=1.98) than in the expanded condition (M=3.97, SD=2.21), F(1.59)=7.91, $p \leq$,05 and harmful in the expanded condition (M=4.75, SD=1.48) than in the regular condition (M=5.59, SD=1.27), F(1,59)=5.55, $p \leq .05$. Participants did not feel that the consent form with the risk terms defined provided more information (M=6.69, SD=1.91) than the consent form without definitions (M=6.76, SD=1.96), F(1, 59)=.89. Participants also did not differ on how well they believed the possible harms of participation were described in the consent form with the definition (M=7.00, SD=1.90) in comparison to the consent form without the definition (M=6.28, SD=6.28), F(1, 59)=.991. There was not a significant difference in how well the participants reported that they understood the consent form with the definition (M=8.34, SD=1.04) versus the consent form without the definition (M=8.55, SD=.78), F(1,59)=.384.

CHAPTER 4: EXPERIMENT THREE

Introduction

The results of Experiment 2 provide evidence that clarifying the risk section of a consent form does not increase the likelihood of consent. In fact, risk section clarification appears to decrease consent rates. According to Epstein and Lasagna, increased consent form understanding is associated with higher consent rates. The results of Experiments 1 and 2 indicate that consent form length does not impact consent rates, and that clarifying risk information leads to lower rates of consent.

No significant difference was found between groups in Experiment 2 on the dimension of understanding, the clarity of the harms section, and the thoroughness of the information provided, suggesting that participants perceive they are knowledgeable about the meaning of the risk terms used in the experimental stimuli. Measures of understanding were based on self-reports, such as those used in Experiment 1. It might be the case that although participants reported no differences in understanding, the addition of a dictionary definition did provide them with information that they were previously unsure of. For example, if a research participant did not understand the meaning of the term "nausea," adding a dictionary definition might create a substantively different risk section for that participant.

To ensure that the participants know the basic meaning of terms like "headache" and "rash," a questionnaire was added to the end of a separate research project where students (N=40) were asked to create definitions for 18 risk terms. The risk terms were the same as those used in the consent forms in

Experiment 1 and 2. The purpose of this questionnaire was to ensure that participants have a basic understanding of the common terms found in the risk sections of clinical consent forms, including those risks listed in Experiment 1 and 2. As the risk terms are commonly found in everyday life, it was expected that this task would not provide any difficulty to university students.

An informal content analysis of the definitions confirmed that students were able to provide accurate definitions of risk terms. Research assistants (N=9) evaluated each term in comparison to a dictionary definition. Although the quality of the writing varied, all participants correctly defined the terms. This finding is consistent with previous research which indicates that participants with a post-secondary education are able to comprehend the majority of the information found in consent forms (Davis et al., 1998).

Research on assessment of risk indicates that people often rely on judgmental heuristics, such as the availability heuristic, when assessing personal risk (Covello, 1983, in Stanley, Sieber & Melton, 1996). Specifically, when participants read and consider risks in research they may rely on the most accessible example of when they have last encountered such a list of risk terms. It may be the case that the information that is most accessible is associated with relatively low risk (e.g., medication, advertising for medication).

It was hypothesized that if participants were encouraged to carefully consider the risks in participation rather than rely on the availability heuristic, the impact on consent rates would be found primarily on research projects that carry higher risk. That is, since high risk studies are more unpleasant and potentially

hazardous to the participant, consent rates should be lower than those in studies with minimal risk. If the possible risks in a study are relatively minimal, focusing on these risks should have little impact on consent rates. The purpose of this experiment was to test the impact of providing risk clarification in high and low risk studies. Experiment 3 built upon the previously discussed work of Slovic et al. (1980) on the use of the availability heuristic in biomedical research.

Method

Participants and Design

Participants were 92 university students who received research credit toward an introductory psychology course requirement. Experimenters were 8 senior undergraduate students.

Procedure

The procedure used a 2 x 2 factorial design. Participants were asked to evaluate a consent form that varied in the detail of the risk section and the risk involved in participation. In the low risk version of the consent form, participants read a procedure in which a muscle dynamometer was used to measure hand strength. The high risk version of the protocol involved a muscle biopsy. Similar to Experiments 1 and 2, the risk sections varied in the amount of detail provided. Within each risk condition, the risk terms were either defined (expanded condition) or only listed (standard condition). See Appendix E for the low risk consent form stimuli and Appendix F for the high risk stimuli. The consent forms presented in the Appendices are the expanded versions. The regular versions are identical, except for the omission of the definition following

each risk term. The dependent measures were similar to those used in Experiment 1 and 2 (See Appendix D).

Results

The hypothesis that expanding risk terms would lead to a decrease in consent rates in high risk research was confirmed. The results of a 2 x 2 between-subjects ANOVA with Risk (high vs. low) and Risk Terms (standard vs. expanded) showed significant main effects on participation rates for Risk ($F(1, 91)=120.80$, $p=.00$), Risk Terms ($F(1, 91)=4.84$, $p\leq.05$) and an interaction effect between Risk and Risk Terms ($F(1, 91)=4.08$, $p\leq.05$) .

Participants were less likely to agree to participate in the high risk condition ($M=2.61$, $SD=1.93$) than in the low risk condition ($M=6.92$, $SD=1.87$), and less likely to consent to the expanded Risk Term condition ($M=5.31$, $SD=2.65$) than the standard Risk Term condition ($M=4.48$, $SD=3.02$). There were no other significant main effects for Risk Term expansion. Participants also found the study presented in the high risk condition to be more harmful ($M=7.90$, $SD=1.42$) than the study presented in the low risk condition ($M=4.72$, $SD=4.72$), $p=.00$; more stressful in the high risk condition ($M=2.62$, $SD=1.68$) than in the low risk condition ($M=6.95$, $SD=1.76$), $p=.00$ and more risky in the high risk condition ($M=2.21$, $SD=1.58$) than in the low risk condition ($M=5.87$, $SD=2.13$), $p=.00$.

An inspection of the interaction means using Tukey's HSD revealed that the participants in the expanded high risk condition were less likely to consent ($M=1.88$, $SD=1.42$) than participants in the standard high risk condition ($M=3.5$,

SD=2.11), $p < .03$. There was no significant difference found in the low risk condition.

Interestingly, post-hoc analysis revealed that consent to participate was the only variable that was affected by the clarification of risk definitions within the high risk condition. On the item "I think that the consent form has enough information to allow people to make a good judgment about whether or not they should participate in this research" there was a marginally significant difference between the high risk clarification definition (M=7.5, SD=1.47) and the high risk standard condition (M=6.2, SD=2.38), $p \leq .10$. No such difference was found in the low risk condition. This item indicates that the addition of a dictionary definition seems to make participants feel that they have been provided with enough information to participate. One concern in Experiment 3 was that risk would be confounded with perceived value of the research. Across all conditions there was no difference found in the perceived value of the research.

CHAPTER FIVE: EXPERIMENT FOUR

Introduction

From the previous experiments, it appears that expanding the definitions of risk terms impacts participant likelihood to consent in high risk studies. The purpose of Experiment 4 was to examine the external validity of the findings. The effect found in Experiment 3 is a subtle one that only seemed to concern consent rates, and not overall perception of the consent form. It is quite different to agree to participate in a hypothetical research project than to agree to actually be involved in research (e.g., Pepler et al., 1993). The goal of this experiment was to replicate the experience of entering into a Phase I clinical trial.

Method

Participants and Design

Participants were 140 university students who received research credit toward an introductory psychology course requirement. Experimenters were 8 senior undergraduate students.

Procedure

The consent forms used in this study were nearly identical to those used in Experiment 4. Minor changes were made to allow the participants the opportunity to provide or deny consent to participate. The participant was met by an experimenter and seated in the lab. The experimenter explained that he or she was interested in the muscular strength of university students and that the study was being conducted jointly by the Department of Psychology and the Department of Physical Therapy at the University of Alberta Hospital. Participants were told that if they decided to participate they would undergo

testing at the University of Alberta Hospital. The hospital is on campus, but is roughly a 15 minute walk from the psychology department. To alleviate students' concern that they would not be able to participate in the study without missing their next class, the experimenter informed them that a shuttle bus would be waiting outside the psychology department to transfer participants to the hospital, and would be available to take them to their next class upon completion of the experiment.

After allowing a brief period for questions, the experimenter explained that because of the limited space at the hospital, the consent procedure would be completed in the lab at the psychology department. The experimenter then handed the participant an envelope containing a consent form, asked them to open it and read the consent form inside carefully, and waited for their decision in a separate part of the lab which was out of view from the participant. Participants were told that the experimenter would be available for questions, but that all relevant information was contained in the consent form. Experimenters were instructed to record all questions asked by the participants. The experimenters were instructed to answer questions only with the information contained in the consent form. The majority of participants did not ask questions, and those who did were only concerned that they would not be able to attend their next class or appointment which they had scheduled after the experiment. Once participants had completed the consent form, they were told to place the consent form in an envelope, seal it, place it in a locked box, gather their belongings and walk towards the shuttle. Although the experimenter was out of the participant's sight,

the locked box was placed such that the experimenter could see if the participant deposited the envelope. If the participant decided not to participate, they were told they could leave, but to notify the experimenter before they did. To ensure that a participant did not leave without being debriefed, the experimenter also listened for movement. If the experimenter heard the door opening, he or she immediately stopped the experiment and fully debriefed the participant. No participant was allowed to leave the lab without a full debriefing.

Ethical Considerations

The dependent measure in this experiment was participant consent. To ensure validity, participants were not provided with the opportunity to give written consent at the onset of the experiment. Before the research began, there was much thought put into how best to conduct the research while ensuring that participants were fully protected. Initially, there was some doubt as to whether an experiment that used the consent form as a dependent measure could be conducted. Article 2.1 (c) of the TCPS addresses this issue:

> 2.1 (c) The REB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth above, or waive the requirements to obtain informed consent, provided that the REB finds and documents that:
>
> i. The research involves no more than minimal risk to the subjects;
>
> ii. The waiver or alteration is unlikely to adversely affect the rights and welfare of subjects;

iii. The research could not practicably be carried out without the waiver or alteration;

iv. Whenever possible and appropriate, the subjects will be provided with additional pertinent information after participation and

v. The waived or altered consent does not involve a therapeutic intervention.

The initial challenge was to be sure that the consent procedure in this research addressed all of the relevant provisions of Article 2.1(c).

A valuable resource in the initial phases of this work was the group of experienced research assistants that were involved in this experiment, the majority of whom had participated in research projects as a component of their introductory psychology class. The research assistants were asked to complete a questionnaire addressing how comfortable they would be if they had to participate in the study, as well as how comfortable they would feel conducting the research. The questionnaire was returned anonymously to the researcher. A group discussion followed. The reason the initial survey was completed anonymously was that many in the research group were friends, and there was concern that an initial open discussion might make some of the research assistants hesitant to voice their opinion. The majority of the comments indicated the need for a thorough debriefing procedure, but that overall everyone felt comfortable with the project.

Through discussion with REB members, my research assistants, and other researchers, the conclusion was that the only way to conduct the study was to waive the written informed consent. Upon completion of the study, participants were provided with the opportunity to withdraw their data. After the experiment was completed, the researcher verbally debriefed the participant, and allowed time for questions. Once the experimenter was confident that the participant understood the nature of the research, the participant was given a post-experimental consent form which explained again why they were not given the opportunity to provide consent before the study began, and the opportunity to withdraw their data without any penalty. Once participants completed this form, they were provided with a written copy of the debriefing form and the phone numbers and e-mail addresses of people to contact if they had any concerns or questions about the research in the future.

Once the REB approved the experiment, a small pilot test was conducted with ten participants. The pilot test involved a description of the study, and a walk-through. The purpose of the pilot test was not to gather data, but to obtain participant's opinions about the suitability of the research. All of the participants in the pilot test felt the project was not harmful, and all recommended that the project continue as planned.

Results

A 2 x 2 (Level of Risk x Risk Terms) ANOVA revealed significant main effects for Risk, $F(1, 136) = 61.89$, $p < .001$ and for expansion of Risk Terms, $F(1, 136) = 6.88$, $p < .01$, and a marginally significant 2-way interaction among

Risk and Length of Consent Form, F (1, 136) = 1.72, p < .192. Inspection of the means for the Risk and Risk Terms main effects revealed that participants were more likely to consent in Low versus High Risk conditions (M=.93 vs. M=.41), and when consent forms were standard versus expanded with a dictionary definition (M=.76 vs. M=.59). While the Risk x Risk Term interaction did not approach conventional levels of significance, inspection of the graph for the interaction (see Figure 1) indicated a tendency for expansion of Risk Terms to have a greater influence on consent in high relative to low risk conditions. Follow-up tests by a Tukey's HSD procedure showed no difference in consent rates for participants in the expanded low-risk condition (M=.89, SD=.32) compared to participants in the standard low-risk condition (M=.97, SD=.17), ns. Participants in the expanded high-risk condition however, were less likely to agree to participate (M=.29, SD=.46) than participants in the standard high-risk short (M=.54, SD=.51), $p \leq .04$.

The effect of Expansion of Risk Terms on consent was enhanced when Risk was high but had little influence when risk was low. Taken together these results indicate that consent was affected by perceptions of Risk and that expansion of Risk Terms influenced decisions when risk was perceived as high. These results indicate that expanding risk terms only impacts the likelihood that a participant will provide consent in high-risk studies. See Figure 2 for consent rates.

Figure 1: Results of Experiment 4

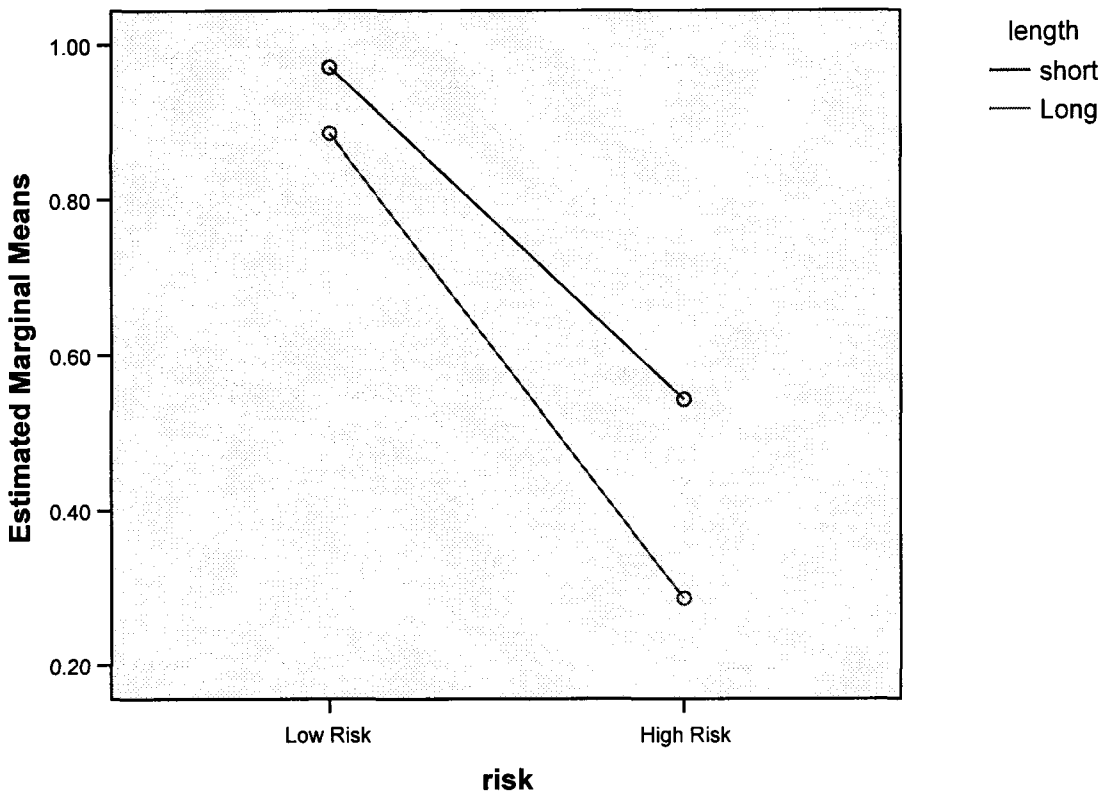
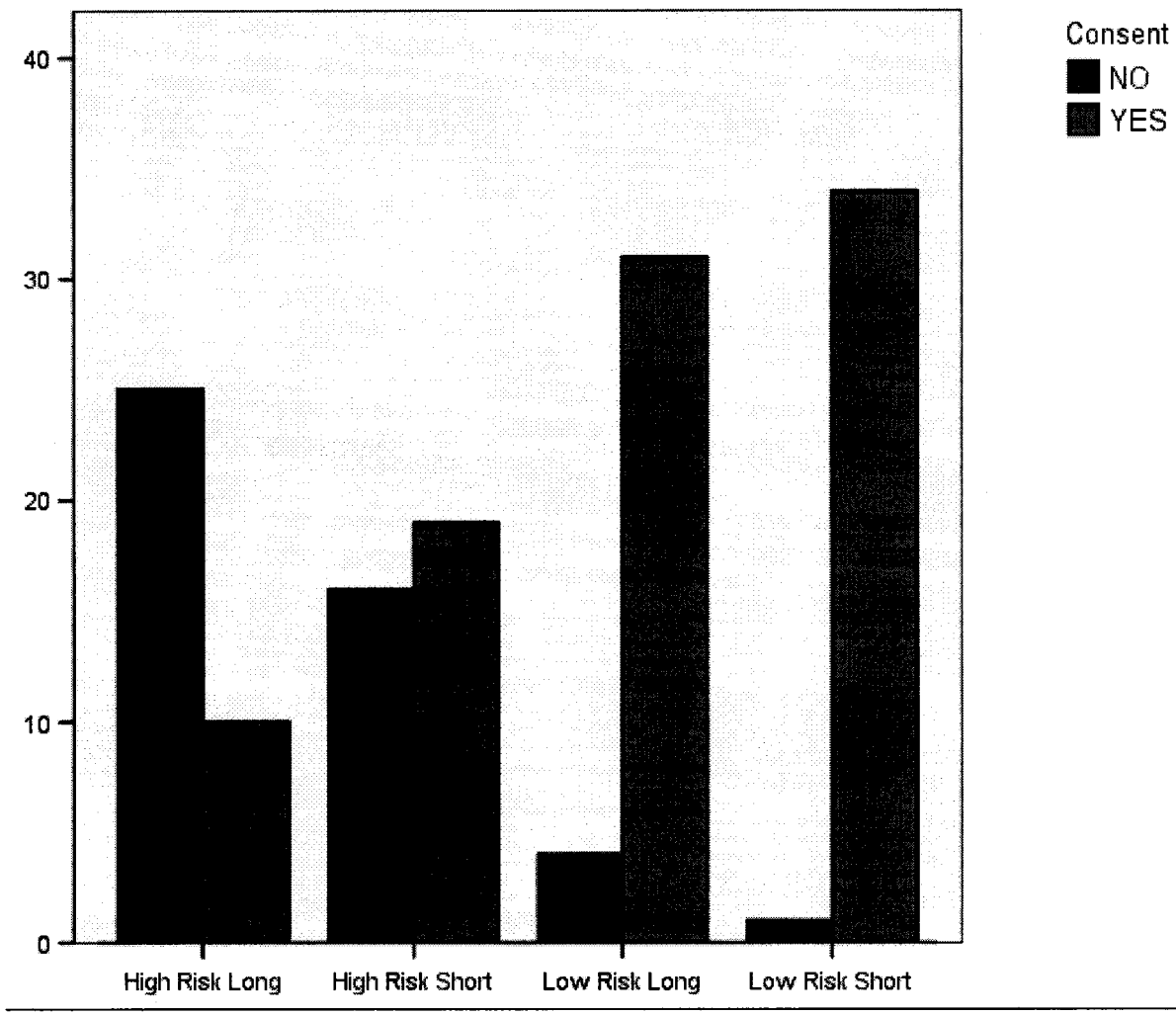


Figure 2. Rates of Consent for Experiment 4



CHAPTER 6: GENERAL DISCUSSION

Summary of Results

The four studies outlined here provide an alternative explanation for the Epstein and Lasagna (1969) conclusions on the impact of consent form length on comprehension and consent, and suggests that participants use the availability heuristic when reviewing consent forms. The results of Experiment 1 indicated that consent form length alone does not influence participant consent rates, nor does length necessarily impact comprehension. Specifically, if a consent form is given additional length without changing the type or amount of risk, the impact is negligible.

The results of Experiment 2 indicated that increasing consent form comprehension does not lead to an increase in consent rates, as predicted by Epstein and Lasagna. In Experiment 2, clarification of risk terms through the addition of dictionary definitions led to a decrease in rates of consent and increased the perceived unpleasantness of the study, while decreasing participants' comfort level with the study. The consent form used in Experiment 2 described considerably more risk than participants are exposed to in an average psychology experiment and, as such, it was expected that participants should not feel overly comfortable with the study. It is reasonable to conclude that the clarification of risk terms led to a more accurate perception of the potential risk associated with participation.

Experiment 3 built upon the work of Slovic et al. (1980) who proposed that the availability heuristic can be used to explain how participants consider risk. The results of Experiment 3 show that in high risk studies, participants are

less likely to give consent if the risk term is clarified, even though the clarification does not increase or decrease understanding of the risk term. Although there are a number of heuristics that participants employ when considering consent (e.g., Lloyd, 2001), these results suggest that participants are relying on the availability heuristic, though possibly not in the way proposed by Slovic et al. Slovic et al. suggested that if participants are presented with a vividly imaginable risk, they will overestimate the likelihood of that risk occurring to them. In Experiment 3, risks were simply clarified with a dictionary definition, and not made vividly imaginable. The consent forms used in Experiment 3 are similar to ones that could be found in an actual clinical trial, where the research of Slovic et al. did not apply directly to the average situation where participants are asked to provide consent. Excluding cases where a major ethical misstep or serious adverse event in a clinical trial have received media attention, participants are not usually provided with a vivid description of risks before they consider consenting to participate in research.

Experiments 1 through 3 involved the use of hypothetical consent scenarios. Participants in these studies understood that they would not be involved in the research described in the consent form and that they were only to imagine what it would be like to consider participation. In Experiment 4, participants were led to believe that they were going to be involved in the research described on the consent form. The results of Experiment 4 indicate that the previous findings in Experiment 3 hold up beyond hypothetical scenarios. The results of this research indicate that clarifying risk information impacts consent

rates in high risk studies, but does not have an impact in low-risk studies. Understanding that participants may use judgmental heuristics when considering consent can help REBs and researchers ensure that participants understand the nature of the research in which they are involved. If properly applied, these findings will contribute to the protection of participants and may decrease attrition rates for researchers.

General Discussion

In Canada, research involving humans generally falls under the auspices of the TCPS [3]. The TCPS outlines the ethical principals that should guide research:

- Respect for human dignity;
- Respect for vulnerable populations;
- Respect for privacy and confidentiality;
- Respect for justice and inclusiveness;
- Balancing harms and benefits;
- Minimizing harm;
- Maximizing benefit; and
- Respect for free and informed consent.

REBs have a myriad of issues to consider and informed consent is only one aspect of the overall protection of human participants, albeit an important one. The TCPS authors note that "free and informed consent lies at the heart of ethical research involving humans" (1998). REB members understand the importance of participants being fully informed before consent is obtained but

they do not have consistent evidence to draw on when evaluating the adequacy of a specific consent form for a clinical trial. This research demonstrates the need to focus on risk, and the role that heuristics may play in ethical decision making. If REB members are aware that this processing is taking place, they should place primary focus on the presentation of risk in the consent form.

REBs do not want to encourage nor discourage participation; the goal of the consent process is to ensure that the participant can make an autonomous decision regarding participation in a clinical trial. By recognizing the type of judgmental strategies that people employ when considering biomedical research, REBs are better able to assess the likelihood that a consent form will be able to inform the participant about the risks of becoming involved in research.

The Focus on Risk

This research focused on how modification of consent forms, specifically the risk section of the form, influences rate of consent. The reason for the focus on risk was twofold. By focusing on the risk section of consent forms, I was able to show that the current literature regarding the impact of length on consent rates is flawed. The focus on risk also highlighted how participants use judgmental heuristics when considering participating in a clinical trial.

Earlier research investigated the impact of manipulating the benefits of research on rates of consent. These early studies indicated that participants generally see research as a positive endeavour, regardless of the benefit to society or themselves (Rodney Schmaltz, unpublished manuscript). In the research on benefit, the initial goal was to identify which types of research participants found

to be most beneficial. Once this was established, there was to be a consent form manipulation similar to that of Experiment 3, except that benefit would be manipulated instead of risk. There was very little variance in how beneficial participants viewed the different types of research. Generally participants see the research endeavour as valuable.

The participants in the studies concerning the degree to which perceived benefits impact consent rates were introductory psychology students with an average age of 19 (Rodney Schmaltz, unpublished manuscript). Future research could investigate if this overly positive view of research is limited to this age cohort. Another possible explanation for these findings is that participants were analyzing hypothetical scenarios, and not ones in which they could actually participate.[4]

The Use of Heuristics

This research focused on how modification of consent forms, specifically the risk section of the form, influences rate of consent. Slovic et al. (1980) have demonstrated that the availability heuristic may be employed when people are considering consenting to participate in research, specifically when there is a vivid account of problems in research. Slovic et al. (1981) claim that providing people with information about a low-probability hazard may increase how easily people can imagine that hazard and lead to an increased concern about risks. While this conclusion may be true in some circumstances, my research suggests that this is not how the availability heuristic is used when a participant is considering the risks in a consent form. Providing people with risk information in

relatively low-risk studies does not impact the likelihood of consent, nor does expanding upon this risk information. In high risk studies, clarifying risk information appears to decrease the likelihood of consent. This difference in consent rates can be explained by the availability heuristic.

On consent forms, the listing of risk terms is similar to the listing of possible side-effects on medication or advertisements for medication, thus the available information regarding risk is associated with low risk. Expanding risk terms with a dictionary definition decreases the reliance on judgmental heuristics in assessing risk. In other words, a participant reading a list of possible risks on a consent form is automatically going to equate that data with information typically seen on a bottle of pills or an advertisement for a medication. That sort of information – usually in small print – does not usually convey any sense of urgency or imminent harm (in fact, many people may simply think of these lists as being there for liability purposes rather than to protect the patient). If such a list of risks is augmented with dictionary definitions then it is no longer comparable to lists with which the patient is familiar (thus, the judgemental heuristic no longer applies in the same manner).

This is not to say that the use of judgmental heuristics is always negative. Heuristics allow for more efficient judgment making, but at the cost of accuracy. In a low-risk study, relying on a judgmental heuristic may allow for a relatively accurate assessment of risk. For example, if the risk terms are similar to those found on a medicine bottle, and the risk is equally low between the risk of participation and the risk of taking a certain medicine, the decision to participate

is not negatively affected by the use of heuristics. In a high-risk study, participants need to carefully consider participation. The use of a judgmental heuristic may hinder this consideration.

The availability heuristic is not the only judgmental heuristic that is employed when participants read and consider the information in a consent form. Previous research has shown that people tend to treat risks on a simple level and tend to be overconfident about the accuracy of their judgments (Lloyd, 2001; Fischhoff, 1982; Slovic, Fischhoff, & Lichtenstein, 1982). Most of the research that has been conducted on the use of heuristics in the consent process has used hypothetical consent forms. Experiment 4 demonstrates an ethically and scientifically viable way to further study how people use judgmental heuristics in the consent process without involving actual patients or relying on the constraints of a particular clinical trial.

Implications for Researchers

As concerns regarding liability increase for both institutions and researchers, it is likely that the length of consent forms will continue to increase. This research demonstrates that increasing consent form length is not necessarily a pressing concern for participants in biomedical research. Although these results imply that participants might be less likely to consent in high risk studies if the consent form is given additional clarification of risk, this is not necessarily a negative outcome for researchers. With all clinical trials, attrition rates are of utmost importance. If during the course of a trial there are high attrition rates, the results may be invalid. High attrition rates might be related to the initial failure of

participants to fully contemplate the risks involved in research. If participants avoid using judgmental heuristics, they might be less likely to be surprised or upset by the actual risks of participation. If participants do not rely on judgmental heuristics, and instead employ deeper processing, the risks involved in research may be considered more accurately.

To investigate this hypothesis, future research will need to build on Experiment 4 by having the participants actually follow through with the research described on a consent form. During the course of the experiment, they will be exposed to one of the risks that had been described earlier. The risk section of the consent form could be manipulated by expanding risk terms, as was done in Experiments 2, 3 and 4. Upon exposure to this relatively benign risk, participants could be asked if they wish to continue in the study. Participants could also be asked to report on how they feel about the research in general. One of the primary difficulties in conducting this research will be to identify risks in a manner that is ethically sound. Future work could also involve archival research looking at the relationship of how consent forms are written and attrition rates in previous clinical trials.

Implications for Multicentre Review

One direct application of this research could be the creation of a standardized consent form for use in research projects conducted across several institutions. There is a pressing need for research on the consent form in order to maintain participant protections and reduce cost in multicentre trials. Currently, human research conducted at institutions receiving funding from any of the three

Canadian federal granting agencies must be reviewed and approved in advance by a qualified human research ethics board at the institution where the work will be conducted. Empirical studies, principally in the United Kingdom, document the very high costs of submitting a single multi-centre protocol to a multiplicity of local ethics review committees. In one often-cited study, Al-Shahi and Warlow report sending nearly 5,789 pages of duplicate application materials to 15 ethics committees for a relatively simple non-clinical trial in Scotland (1999). Humphreys et al. conducted a cost audit of supplemental ethics committee reviews after the first of eight reviews conducted for a multi-centre study of substance abuse treatment. They report that the additional reviews cost, in 2001 US dollars, $56,191. In the United States and Great Britain, there is considerable evidence that ethics committees require an extraordinary range of time to review exactly the same protocol, ranging from a few days to a year in some cases (Larson et al., 2004). Anecdotal evidence abounds that the same is true in Canada. Much of this cost lies in revision to consent forms. Some REBs will accept a consent form, whereas others will demand changes; even the type and extent of changes requested is not consistent across REBs (Silverman, Hull & Sugarman, 2001). The changes are not demanded as the result of an analysis of empirical evidence on the consent process, rather they are based on good intentions (e.g., Paul, 2000).

To alleviate these costs, and increase approval times, centralized review systems have been adopted where a single REB reviews a protocol that will be carried out at a number of institutions (e.g., within the United Kingdom).

Although such a system is not nationally in place in Canada, there is discussion that a similar system may soon be implemented. If a centralized system were adopted in Canada, there would be a need for standardized consent form templates (for an example of a standardized consent form template, see: http://www.med.mun.ca/hic/forms.htm). This means that one consent form would be used across all institutions involved in any given multicentre trial. In comparison to the impact of a poor consent form on a single trial, the impact of flaws in a consent form for multicentre research will be magnified as significantly more participants may unnecessarily be restricted from making an informed and autonomous decision. The adoption of a centralized review system will reduce costs and approval time for researchers, without the loss of protections for participants. If the consent form used in the trial leads to any potential harms, this could cause institutions to opt out of the centralized review system, and cause the system to fail. Failure of the system will impede potentially valuable research.

Application to the Social Sciences

The focus of this research was on biomedical trials. This was primarily the case because the research was born out of interest in developing the best possible consent form for use in multicentre trials. The general findings that participants use judgmental heuristics when assessing risk apply to the social sciences as much as the biomedical sciences, however the social sciences present a unique set of issues that require further study. The range of what is considered an acceptable consent form varies widely in the social sciences. Research in the social sciences is broad, incorporating everything from large scale marketing

studies to research on aboriginal culture. It is difficult to imagine a standardized form, or even a set of templates, that could apply to all types of research in the social sciences.

Although there may not be a direct application of the results of this research to a standardized or perfect consent form for the social sciences, the finding that participants are using judgmental heuristics when processing risk does have vital implications. It is important that participants are able to make a fully informed decision about participation, and as such should be provided with clarifying information regarding risk (even if that risk is not physical in nature). Unfortunately, foreseeable risk in participation can be extremely difficult to predict in much of the work within the social sciences. For example, in a study conducted using an open interview, the researcher does not have control of what the participant might begin to discuss. Researchers are presented with a problem in the consent process of deciding what to include. If participants are told that they might discuss something that is troublesome to them, it could potentially prime them to focus on these types of issues. This priming effect could potentially lead to increased harms and validity issues within the research. If participants are not made aware that the discussion could be potentially troublesome, one could argue that they are not provided with enough information to make a fully informed decision.

Follow up research on the social sciences could investigate this potential priming effect. Participants could be presented with a set of potential risks in a consent form for a study that will involve discussion. It would be interesting to

see if listing the risks leads people to focus more heavily on those risks. If it is the case in the social sciences that by listing a risk, a participant is more likely to experience that risk, there is considerable work to be done to better understand how to allow participants to make an autonomous decision regarding consent without potentially exposing them to additional harms.

Additional Future Research

In addition to the studies that have been proposed here using the experimental paradigm of Experiment 4, upcoming research could investigate other crucial issues such as the impact of participant trust on rates of consent. Gertson et al. (1984) found that willingness to participate in a clinical trial depended largely upon the physician who provided them with information regarding the trial. In my research, the experimenters were carefully trained to remain consistent across trials. In the future, research could be conducted to investigate experimenter variables that impact consent.

Another factor that may affect the willingness of participants to "trust" the research (and, therefore, provide consent) has to do with the identified sponsor of the research. Previous work conducted by Schmaltz & Enzle (unpublished manuscript) failed to find any effect for manipulating study sponsor on rates of consent. In our research we had participants read hypothetical consent forms for a clinical drug trial that was either sponsored by Health Canada or a pharmaceutical company. While participants reported that they felt Health Canada was more trustworthy than a pharmaceutical company, it did not result in differences to

consent to participate in a hypothetical study. This experiment could be replicated using the methodology described in Experiment 4.

As discussed earlier, some research on the consent process treats participants in research and patients undergoing treatment as interchangeable. The results of this research apply primarily to the consent process in biomedical research. Follow up studies could be conducted to see if similar effects are found in the informed consent process for treatment.

Conclusions

Although much research has been done on consent, no one has been able to suggest what the ideal consent form should look like. There is still conflicting evidence regarding the information that should be included on a consent form to ensure that participants are best able to make a fully informed and autonomous decision (e.g., Edwards et al., 1998). While the consent form is only one component of the overall consent process, its importance cannot be overstated. Anyone who has had the experience of visiting a hospital for treatment understands the demands placed on physicians, some of whom are also conducting research. Physicians carry heavy workloads and they try to deal with patients as quickly as possible (which is not to say that patients are necessarily treated poorly, rather physicians are attempting to maximize efficiency). Similarly, anyone who has had the experience of visiting a hospital for treatment understands the demands that they experience as a result of requiring diagnosis or treatment. Being cast in the role of research participant, as well as patient, can

increase the difficulty associated with evaluating information concerning participation in a study.

As physicians and researchers are increasingly pressed for time, the consent document will be the primary source of information for someone considering participation for a clinical trial (M. Enzle, personal communication). To protect participants, it is crucial that the consent form provide the necessary information to allow them to make a truly informed and voluntary decision about entering a research project. This research provides investigators and REBs with additional information to consider when ensuring that the consent document allows for a full and autonomous decision regarding research participation.

Footnotes

[1] Although there is some criticism of the lack of researcher involvement in this process, Faden (1977) has found that this disclosure model is practical and no less effective than a one-on-one formal discussion, a videotape providing additional information, or an informal discussion.

[2] Other examples included: Epstein and Lasagna's (1969) finding that increasing the amount of information in a consent form increases anxiety, while Denny, Williamson, & Penn (1976) found that additional information did not have an impact on reports of anxiety; Fetting et al. (1990) found that descriptive information led to higher rates of consent than numerical information, whereas Llwewllyn-Thomas, 1995) failed to replicate this effect. Additional examples can be found in Edwards et al. (1998) literature review on the consent process.

[3] It is generally recognized that while the TCPS does not have the status of legislation, there is reason to believe that - in the absence of a national standard - the TCPS would be assumed to establish minimum standards for the protection of humans in research in Canada (Hadskis & Carver, 2005).

[4] An interesting example of the difference between behaviour and the responses to hypothetical scenarios can be found in the work conducted by Pepler, Craig, Zeigler, and Charach (1993). Pepler et al. asked children how they felt about bullying and what they would do if they encountered another child being bullied. 88% of the children said that it was unpleasant to watch, 70-80% said they wouldn't join in, and about 50% said they would intervene to help the victim.

Pepler and Craig (1995) then recorded bully, victim, and peer behaviour with a remote video camera and a wireless microphone that each child wore. Children actually participated with the bully in 85% of the instances. Sometimes the children just watched or verbally encouraged the bully's actions, but in almost 50% of the instances, they actively participated with the bully.

References

Adair, J.G. (2001). Ethics of psychological research: new policies; continuing issues; new concerns. *Canadian Psychology, 42(1),* 25-37.

Al-Shahi, R., & Warlow, C.P. (1999). Ethical review of a multi-centre study in Scotland: a weighty problem. *Journal of the Royal College of Physicians of London, 33*, 549.

American Psychological Association. (2002). Ethical principles of psychologists and code of conduct. Washington, DC: Authors.

Annas, G. J., Glantz, L. H., & Katz, B. F. (1977). *Informed consent to human experimentation: The subject's dilemma.* Cambridge MA: Ballinger.

Baumrind, D. (1964). Some thoughts on the ethics of research: On reading Milgram's "Behavioral study of obedience". *American Psychologist*, 19, 421-423.

Byrne, D., Napier, A., & Cushieri, A. (1988). How informed is signed consent? *British Medical Journal, 296,* 839-841.

Canadian Psychological Association (1991). *Canadian Code of Ethics for Psychologists.* Ottawa, ON.

Cassileth, B.R., Zupkis, R.V., Sutton-Smith, K., March, V. (1980). Informed consent – why are its goals imperfect realized? *New England Journal of Medicine, 302(16),* 896-900.

Chee Saw, K., Wood, A.M., Murphy, K., Parry, J., & Hartfall, W. (1994). Informed consent: An evaluation of patients' understanding and opinion (with respect to the operation of transurethral resection of prostate). *Journal of the Royal Society of Medicine, 87,* 143-144.

Covello, V. (1983). The perception of technological risks: A literature review. *Technological Forecasting and Social Change, 23*, 285-297.

Davis, S., Seay, J., Stone, J., et al. (1990). Does knowing about clinical trials increase participation? *Proceedings of the American Society for Clinical Oncology, 9,* A232.

Davis, T., Holcombe, R., Berkel, H., Pramanik, S., & Divers, S. (1998). Informed consent for Clinical Trials: a Comparative Study of Standard Versus Simplified Forms. *Journal of the National Cancer Institute, 90(9),* 668-674.

Dawes, P.J., O'Keefe, L., Adcock, S. (1993). Informed consent: Using a structured interview changes patients' attitudes towards informed consent. *Journal of Laryngology and Otology, 107(9),* 775-779.

Department of Health, Education, and Welfare. (1979). *The Belmont Report,* DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014. Washington, DC: U.S. Government Printing Office.

Edwards, S., Lilford, R., Thornton, J., Hewison, J. (1998). Informed consent for clinical trials: In search of the "best" method. *Social Science & Medicine, 47,* 1825-1840.

Epstein, L. & Lasagna, L. (1969). Obtaining informed consent. *Archives of Internal Medicine, 123,* 682-688.

Enzle, M.E. & Schmaltz, R. *National human ethics review and stem cell research.* Paper presented at the Symposium on Bill C-56: The Assisted Human Reproduction Act. Sep. 21, 2002.

Eyler, L., & Jeste, D. (2006). Enhancing the informed consent process: a conceptual overview. *Behavioral Sciences & the Law, 24(4),* 553-568.

Faden, R.R. (1977). Disclosure and informed consent: Does it matter how we tell it? *Health Education Monographs, 5(3),* 198-214.

Faden, R. R., & Beauchamp, T. L. (1980). Decision-making and informed consent: A study of the impact of disclosed information. *Social Indicators Research, 7,* 313-336.

Finney, P. D. (1984). Coparticipant effects on subjects' decisions to consent for risk-involving research. *Journal of Social Psychology, 124,* 35-41.

Fischhoff, B. (1982). Debiasing. In D. Kahneman, P. Slovic, & A. Tversky (Eds.), *Judgment under uncertainty: Heuristics and biases* (pp. 422-444). Cambridge: Cambridge University Press.

Gallo, C., Perrone, F., De Placido, S., Giusti, C. (1995). Informed vs. randomized consent to clinical trials. *Lancet, 346,* 1060-1064.

Gertson, L. L., & McNamara, J. R. (1984). Factors influencing a person's reaction to informed consent. *Psychological Reports, 54(1),* 112-114.

Gigerenzer, G., & Goldstein, D. (1996). Reasoning the fast and frugal way: Models of bounded rationality. *Psychological Review, 103(4),* 650-669.

Goldstein, A.O., Frasier, P., Curtis, P., Reid, A., & Kreher, N.E. (1996). Consent Form Readability in University-Sponsored Research. *Journal of Family Practice, 42(6),* 606-611.

Grossman, L., & Summers, F. (1980). A study of the capacity of schizophrenic patients to give informed consent. *Hospital and Community Psychiatry, 31,* 205-206.

Health Canada, (2004). *Therapeutic Products Directorate.* Retrieved April 5, 2004 from http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_drugs_information_forms_e.html.

Hadskis M., Carver P. (2005). The Long arm of administrative law: Applying administrative law principles to research ethics boards. *Health Law Review, 13,* 2-3.

Hopper, K.D., TenHave, T.R., Hartzel, J. (1995). Informed consent forms for clinical and research imaging procedures: how much do patients understand? *American Journal of Roentgenology, 164(2),* 493-496.

Holmes, C., Margetts, J., & Gibbs, G. (1979). Who should decide? A survey of attitudes about bioethical decision-making. *Ethics in Science and Medicine, 6,* 137-144.

Humphreys, K., Trafton, J., Wagner, T. H. (2003). The cost of institutional review board procedures in multi-centre observational research. *Annals of Internal Medicine, 139,* 77-77.

International Conference on Harmonisation. *Good clinical practice guidelines.* [on-line] Available: http://www.ncehr-cnerh.org/english/gcp/

Joffe, S., Cook., F., Cleary, P., Clark, J. & Weeks, J. (2001). Quality of informed consent: A new measure of understanding among research subjects. *Journal of the National Cancer Institute, 93(2),* 139-147.

Larson, E., Bratts T., Zwanziger, T.J. & Stone, P. (2004) A survey of IRB process at 68 U.S. hospitals. *Journal of Nursing Scholarship, 36,* 260-264.

Lavori, P.W., Sugarman, J., Hays, M., & Feussner, J.R. (1999). Improving informed consent in clinical trials : A duty to experiment. *Controlled Clinical Trials, 20,* 187-193.

Lankton, J.W., Batchelder, B.M., & Ominsky, A.J. (1977). Emotional responses to detailed risk disclosure for anesthesia, a prospective, randomized study. *Anesthesiology, 46,* 294-296.

Lloyd, A.J. (2001). The extent of patients' understanding of the risk of treatments. *Quality in Health Care, 10,* i14-i18.

LoVerde, M.E., Prochazka, A.V., & Byyny, R.L. (1989). Research consent forms: continued unreadability and increasing length. *Journal of General Internal Medicine, 4(5),* 410-412.

McDonald, M. et al. (2000). *The governance of health research involving human subjects.* Ottawa: Law Commission of Canada.

Medical Research Council of Canada [now Canadian Institutes of Health Research], Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.* Ottawa: Public Works and Government Services Canada, 1998.

Memorial University of Newfoundland, Human Investigation Committee, *General HIC Application Form and Checklist.* [on-line] Available: http://www.med.mun.ca/hic/forms.htm.

Milgram, S. (1974). *Obedience to authority.* New York: Harper & Row.

Myers, M., Cairns, J., & Singer, J. (1986). The consent form as a possible cause of side effects. *Clinical Pharmacology & Therapeutics, 42,* 250-253.

Nisbett, R. E., & Ross, L. (1980). *Human inference: Strategies and shortcomings of social judgement.* Englewood Cliffs NJ: Prentice-Hall.

Office of Human Subjects Research. (1949). Nuremberg Code. *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2.* Washington, DC: U.S. Government Printing Office.

Patel, A., Wilke, H., Mingay, D., Ellis, J. (2004). Patient attitudes towards granting consent to participate in perioperative randomized clinical trials. *Journal of Clinical Anesthesia, 16,* 426-434.

Paul C. (2000). Health researchers' views of ethics committee functioning in New Zealand., *New Zealand Journal of Medicine, 113(1111),* 210-241.

Pepler, D. J. & Craig, W. M. (1993). School-based social skills training with aggressive children: Necessary, but not sufficient? *Exceptionality Education Canada, 3,* 177-194.

Pepler, D. J. & Craig, W. M. (1995). A Peek Behind the Fence: Naturalistic observations of aggressive children with remote audiovisual recording. *Developmental Psychology, 31*, 548-553.

Silverman H., Hull S.C., & Sugarman J. (2001) Variability among institutional review boards' decisions within the context of a multicenter trial. *Critical Care Medicine, 29(2),* 235-41.

Simes, R.J., Tattersall, M.H.N., Coates, A.S., Raghavan, D., Solomon, H.J., & Smartt, H. (1986). Randomised comparison of procedures for obtaining informed consent in clinical trials of treatment for cancer. *British Medical Journal, 293,* 1065-1068.

Slovic, P., Fischhoff, B., Lichtenstein, S. (1980). Informing people about risk. In L. Morris, M. Mazis, & B. Barofsky (Eds.), *Product labeling and health risks: Banbury Report 6* (pp.165 – 181). Cold Spring Harbor NY: Cold Spring Harbor Laboratory.

Slovic, P., Fischhoff, B., Lichtenstein, S., & Roe, F. J. (1981). Perceived risk: psychological factors and social implications. *Proceedings of the Royal Society of London. Series A, Mathematical and Physical Sciences, 376(1764),* 17 – 34.

Slovenko, R. (1999, July-August). Why study informed consent? [Letter to the editor]. *Hastings Center Report,* p. 4.

Stanley, B., Sieber, J. E., & Melton, G. B. (1987). Empirical studies of ethical issues in research. *American Psychologist, 42(7),* 735 – 741.

Stanley, B. H., Sieber, J., & Melton, G., B. (1996). *Research ethics. a psychological approach.* Lincoln,. NB: University of Nebraska Press.

Stuart, R. B. (1978). Protection of the right to informed consent to participate in research. *Behaviour Research and Therapy, 9*, 3-82.

Tindall, B., Forde, S., Ross, M. W., Goldstein, D., Barker, S., Cooper, D. A. (1994). Effects of two formats of informed consent on knowledge amongst persons with advanced HIV disease in a clinical trial of didanosine. *Patient Education and Counselling, 24(3),* 261-266.

Tversky, A. & Kahneman, D. (1973). Availability: A heuristic for judging frequency and probability. *Cognitive Psychology, 5*, 207-232.

Verheggen, F., & Wijmen, F. (1996). Informed consent in clinical trials. *Health Policy, 36*, 131-153.

Wagner, L., Davis, S., & Handelsman, M.M. (1998). In search of the abominable consent form: The impact of readability and personalization. *Journal of Clinical Psychology, 54,* 115-120.

White, D. R., Muss, H. B., Michielutte, R., Cooper, M. R., Jackson, D. V., Richards, F., et al. (1984). Informed consent: Patient information forms in chemotherapy trials. *American Journal of Clinical Oncology: Cancer Clinical Trials*, 7, 183-190.

World Medical Organization. (1996). Declaration of Helsinki. *British Medical Journal, 313(7070),* 1448-1449.

Ziker, D. (2003). Reviving informed consent: Using risk perception in clinical trials. *Duke Law and Technology Review.* 2003.

Appendix A: Advertisement for Medication

Advertisement removed due to copyright restrictions.

Appendix B Short Form

Patient's Initials .....

UNIVERSITY OF ALBERTA

CONSENT FORM

TITLE: **A Multicentre, Double-Blind, Randomized, Flexible-Dose, Placebo-Controlled Study of Zolpidem in Patients with Major Insomnia**

PRINCIPAL INVESTIGATOR: **Telephone:**
CO-INVESTIGATORS: **Telephone:**

Purpose

You are being invited to participate in a research study. Your decision about whether or not to participate is completely voluntary.

The purpose of this study is to test whether the drug zolpidem is safe and effective in the treatment of major insomnia, and whether there are significant side effects of the medicine. Zolpidem will be compared with placebo (a capsule that looks exactly like zolpidem but that contains no active drug).

Zolpidem is a new investigational drug; it has not yet been approved by Health Canada for doctors to prescribe. It has been tested in over 200 patients so far with major insomnia and has also been tested in healthy human volunteers.

The present study involves 3 phases, lasting up to 15 weeks and involving up to 11 visits to the sleep clinic.

Please read the remaining sections before you decide whether or not to take part in the research study. Ask the study doctor or nurse, to talk with you about anything that you do not understand, or about any questions you have. You do not have to decide right now to participate.

Procedures:

Every day for the first 11 weeks of the study you will be asked to complete a diary recording your sleep patterns, including whether you difficulty falling asleep, remaining asleep or any related symptoms (e.g., general anxiety, trouble staying awake, etc.). The doctor will review the diary with you at each study visit. You will be contacted by telephone once a week for the first 4 weeks of the study to remind you to complete the diary and to see if you have any questions.

After the study is complete, you will no longer take the study medication. Currently, zolpidem is not available for use outside of research studies like this one. Your doctor will decide with you, what medicine would be best for you to be treated with after you are done the study.

Benefits of taking part in the study:
There is a possibility that your condition may improve and that your participation in this study may help develop an improved treatment for others insomnia.

Risks of taking part in the study:
People taking zolpidem have experienced side effects. Most common were:

- daytime drowsiness
- dizziness
- lightheadedness
- constipation
- diarrhea
- dry mouth
- Although unlikely, this drug can cause memory loss
- A serious allergic reaction to this drug is unlikely, but could include:
    - rash
    - itching
    - swelling
    - trouble breathing

Risks to women able to have children.:
Pregnant or breast feeding women may not take part in the study, because the risk to an unborn or breast-fed child is not known. Women of child-bearing potential must use an effective method of birth control during the study.

Right to Withdraw:
You may choose not to take part in this study. You are free to withdraw from the study AT ANY TIME and for any reason.

Confidentiality:
Personal records relating to this study will be kept confidential.

Questions and Concerns About the Study:
You can ask the research staff about the study at any time. If you think you have an injury or bad reaction to the study medicine, you should contact..... ...In an emergency, they can be reached through the You can also contact one of the other study doctors. They can be reached through

Appendix C: Standard Form

Patient's Initials .....

UNIVERSITY OF ALBERTA

CONSENT FORM

TITLE: **A Multicentre, Double-Blind, Randomized, Flexible-Dose, Placebo-Controlled Study of Zolpidem in Patients with Major Insomnia**

PRINCIPAL INVESTIGATOR: **Telephone:**
CO-INVESTIGATORS: **Telephone:**

Purpose

You are being invited to participate in a research study. Your decision about whether or not to participate is completely voluntary.

The purpose of this study is to test whether the drug zolpidem is safe and effective in the treatment of major insomnia, and whether there are significant side effects of the medicine. Zolpidem will be compared with placebo (a capsule that looks exactly like zolpidem but that contains no active drug).

Zolpidem is a new investigational drug; it has not yet been approved by Health Canada for doctors to prescribe. It has been tested in over 200 patients so far with major insomnia and has also been tested in healthy human volunteers.

The present study involves 3 phases, lasting up to 15 weeks and involving up to 11 visits to the sleep clinic.

Please read the remaining sections before you decide whether or not to take part in the research study. Ask the study doctor or nurse, to talk with you about anything that you do not understand, or about any questions you have. You do not have to decide right now to participate.

Procedures:

Every day for the first 11 weeks of the study you will be asked to complete a diary recording your sleep patterns, including whether you difficulty falling asleep, remaining asleep or any related symptoms (e.g., general anxiety, trouble staying awake, etc.). The doctor will review the diary with you at each study visit. You will be contacted by telephone once a week for the first 4 weeks of the study to remind you to complete the diary and to see if you have any questions.

Screening Phase (two weeks).
The purpose of this phase is to see if you are eligible to take part in the study.

Visit 1
During your first visit with the study doctor the following will occur:

-the doctor will ask you about past illnesses, drug sensitivities, the medication that you are taking currently and have taken in the past etc.
-the doctor will review your symptoms to confirm that you have major insomnia
-a physical examination, including height and weight, and vital signs (heart rate, blood pressure, and breathing rate-- no internal examinations will be performed)
-you will be asked to complete questionnaires to measure insomnia and any effects of it on your daily activity
-electroencephalogram, a measurement of the electrical activity of the brain)
-urine tests to assess general health and to check what drugs are in your system, including prescription medication and illegal or street drugs; this is important for your safety, since some drugs may interact badly with the study medication, possibly leading to serious side effects. You will be told about the results and the information will be confidential.
-routine blood work to test general health (1-2 Tbsp of blood will be drawn); a portion of the blood from patients who could become pregnant will be used for a pregnancy test

Visit 2.
This visit involves the following procedures:
-questionnaires to measure insomnia and its effects on your lifestyle, including work, sexual function, daily activities and sleep
-review of any changes in your health or concerns and any medication you have been taking
-review of your diary
-vital signs (heart rate, blood pressure, breathing rate)

If you meet the requirements to continue in this study, you will be given study capsules at this visit.

Phase II. Study Capsules (8 weeks)
You will be assigned, by chance (like tossing a coin) take either the study medication zolpidem or a placebo (an identical looking capsule that does not contain any active medicine).

You will be asked to take 1 to 2 capsules once a day (in the evening, prior to your usual rest time). You will have an equal chance of receiving one of the treatments, which means you have a 1 in 2 (50%) chance of receiving placebo.

Visits 3 – 7
-questionnaire (to measure sleep patterns)
-review health changes or concerns and medications taken
-review diary
-check vital signs

In addition to the above, some of the visits involve extra procedures:

Visit 4
-urine drug screen

Visit 6
-urine sample for general health and drug screen as at Visit 1
-blood sample (1-2 Tbsp.) to check general health
- electroencephalogram
-questionnaires to assess effects on your condition on work and daily activity

Visit 8
-review health changes or concerns and medications taken
-urine sample to check general health and drug screen as performed at your first visit
-blood sample (1-2 Tbsp.) to check general health and pregnancy test for all females who could become pregnant

<u>After Visit 8 you will stop taking the study capsules.</u>

Visit 9 (Follow-up)
-review health changes or concerns and medications taken
-check vital signs
-blood sample (1-2 Tbsp.) and urine sample taken only if the study doctor feels it necessary.

If you started study medication but ended the study early, you will be asked to come for a final visit, involving the procedures for Visit 8. The purpose of this Visit is to check your health and obtain information for the study. You do not have to come back, though.

Phase III. Extension Study (4 weeks)
If you have completed all 9 study visits, and did not experience any serious side effects, at visit 9 you may be invited to take part in an extension phase for up to 4 more weeks. The purpose is to collect more information about the safety of zolpidem. All patients will receive zolpidem. You will be given the study medication at Visit 9. Please note that you may have been receiving placebo in phase II and should therefore take precautions (see risks section below) with the first few doses during this phase.

Visit 10
-review health changes or concerns and medications taken
-check vital signs

Visit 11
-review health changes or concerns and medications taken
-check vital signs
-electroencehalgram
-blood sample (1-2 Tbsp.) and urine sample

After the study is complete, you will no longer take the study medication. Currently, zolpidem is not available for use outside of research studies like this one. Your doctor will decide with you, what medicine would be best for you to be treated with after you are done the study.

Benefits of taking part in the study:
There is a possibility that your condition may improve and that your participation in this study may help develop an improved treatment for others insomnia.

Risks of taking part in the study:

Side effects of zolpidem:

People taking zolpidem have experienced side effects. Most common were:

- daytime drowsiness
- dizziness
- lightheadedness
- constipation
- diarrhea
- dry mouth
- Although unlikely, this drug can cause memory loss
- A serious allergic reaction to this drug is unlikely, but could include:
    - rash
    - itching
    - swelling
    - trouble breathing

Risks to women able to have children.:

Pregnant or breast feeding women may not take part in the study, because the risk to an unborn or breast-fed child is not known. Women of child-bearing potential must use an effective method of birth control during the study. The study doctor will advise what methods can be used. If you think that you have become pregnant during the study, please contact the study doctor. You will be removed from the study, but you and your baby's health will be monitored throughout your

pregnancy. Even with a normal delivery and birth, unknown future problems may occur as the child develops and we would advise you to remain aware of this throughout the childhood years.

Other risks:

The experience with zolpidem in humans is limited. Use of zolpidem could involve new risks or new and unknown side effects or unexpected effects when taken with other medications. It is possible that you may not get any help from taking the study medication. There is a possibility that your condition may worsen over time. In that case, your study treatment will be stopped. Your study doctor will talk with you about other treatments and your treatment will be changed.

All the medical tests in this study are routine. Only a small amount of blood (a maximum of about 10 tablespoons) is taken for the blood tests. There is a risk of mild pain, bruising, fainting, or rarely infection from having blood drawn.

Restrictions:

While in this study, you will not be allowed to take certain medications, because they may lead to harmful interactions with the study drug or may interfere with the research results on the study drug. You will not be allowed to take sodium oxybate, rifampin, anti-anxiety drugs, anti-seizure drugs, muscle relaxants, narcotic pain relievers, psychiatric medicines, or tranquilizers. The study doctor will discuss this with you in more detail.

For the first 11 weeks of the study, you will not be allowed to take medication (including prescription, non-prescription or natural remedies) other than the study medication to treat your sleep disorder. If you can not tolerate your insomnia, though, your study doctor will withdraw you from the study and prescribe other therapy.

For your safety, you must tell the study doctor about all medications you are taking, including herbal or "natural" remedies, and to check with the study doctor before you begin taking a new medication while in this study. Zolpidem may affect your thinking and judgment skills. You should not operate machinery, including driving a car, until you know how your performance is affected. Alcohol should be avoided or used in moderation. Please use the study medicine only as prescribed. Only you should take it.

New Developments:

You will be told of any new findings that might change your decision to take part in the study.
Right to Withdraw:

You may choose not to take part in this study. You are free to withdraw from the study AT ANY TIME and for any reason. Your doctor will continue to treat you. Your doctor has the right to withdraw you, if he/she thinks that this is in your best interest, if there are problems following the procedures, or there is new information about the study medicine (such as new side effects). The study may be stopped by the drug company or regulatory agencies.

Further Therapy:
You do not have to take part in this study to receive treatment for your insomnia.

Compensation:
There will be no monetary costs to you for participating in this study. You will not be charged for the study drug(s) or any research procedures. If you become ill or injured as a direct result of taking part in this study, necessary medical treatment will be available at no additional cost to you. By signing this consent form you are not releasing the investigator(s), institutions(s) and/or sponsor(s) from their legal and professional responsibilities.

Confidentiality:

Your medical records will indicate your participation in this study. Personal records relating to this study will be kept confidential. However, in addition to the investigators, the sponsoring drug company will have access to your records. Any report published as a result of this study will not identify you by name.

Questions and Concerns About the Study:

You can ask the research staff about the study at any time. If you think you have an injury or bad reaction to the study medicine, you should contact.....In an emergency, they can be reached through the You can also contact one of the other study doctors. They can be reached through

Appendix D

Questionnaire

INSTRUCTIONS: Please circle a number on each scale to indicate your answer. Consider what you have just read, and try to answer each question as accurately as possible. All of your answers to these questions are completely anonymous and confidential and cannot be matched up with your name.

Would you participate in this research (if you had insomnia)?

Definitely No 1 2 3 4 5 6 7 8 9 Definitely Yes

How valuable do you think this research would be to the medical treatment of insomnia?

Not at all Valuable 1 2 3 4 5 6 7 8 9 Very Valuable

How free do you believe readers of the Consent Form felt to refuse to participate?

Not at all Free 1 2 3 4 5 6 7 8 9 Completely Free

How much personal harm do you think you would experience if you were to participate in the "Study of Zolpidem" research project ?

Great Harm 1 2 3 4 5 6 7 8 9 No Harm

How stressful do you think it would be to participate in the "Study of Zolpidem" research project ?

Not at all Stressful 1 2 3 4 5 6 7 8 9 Very Stressful

How unpleasant do you think it would be to participate in the "Study of Zolpidem" research project?

Very Unpleasant 1 2 3 4 5 6 7 8 9 Pleasant

Do you agree that the Consent Form for the "Study of Zolpidem" research project provided people with enough information to make a reasonable decision to volunteer, or not to volunteer, to participate?

Strongly Disagree 1 2 3 4 5 6 7 8 9 Strongly Agree

Do you think the Consent Form was well done, was well-written?

Very Poorly Done 1 2 3 4 5 6 7 8 9 Very Well Done

Do you think that most people with a high school education would fully understand the Consent Form?

Definitely No 1 2 3 4 5 6 7 8 9 Definitely Yes

In research of this nature, how important do you think it is that people are given a chance to consent to participate?

Not Very Important 1 2 3 4 5 6 7 8 9 Very Important

How do you feel about the length of the Consent Form?

Not Long Enough 1 2 3 4 5 6 7 8 9 Far Too Long

How clear would you say the Consent Form for the "Study of Zolpidem" research project was?

Not very Clear	1	2	3	4	5	6	7	8	9 Very Clear

How well would you say the possible benefits of the research were described in the Consent Form?

Very Poorly	1	2	3	4	5	6	7	8	9 Very Well

How well would you say the possible harms of the research were described in the Consent Form?

Very Poorly	1	2	3	4	5	6	7	8	9 Very Well

How much do you agree with the following statements regarding the "Study of Zolpidem" research project?

I would feel comfortable participating in this research.

Strongly Disagree	1	2	3	4	5	6	7	8	9 Strongly Agree

I think people would be more likely to participate in this research if the Consent Form contained more detail.

Strongly Disagree	1	2	3	4	5	6	7	8	9 Strongly Agree

I believe that the Consent Form was fine the way it was.

Strongly Disagree	1	2	3	4	5	6	7	8	9 Strongly Agree

I believe the research project described in the Consent Form was valuable.

Strongly Disagree	1	2	3	4	5	6	7	8	9 Strongly Agree

I understood the Consent Form

Strongly Disagree	1	2	3	4	5	6	7	8	9 Strongly Agree

If a research project is very important, I think it's okay if some minor harm comes to the people who participate in it.

Strongly Disagree	1	2	3	4	5	6	7	8	9 Strongly Agree

I believe that most people who suffer from insomnia would participate in this research.

Strongly Disagree	1	2	3	4	5	6	7	8	9 Strongly Agree

I believe that most people did not fully understand the Consent Form

Strongly Disagree	1	2	3	4	5	6	7	8	9 Strongly Agree

The Consent Form was poorly done.

Strongly Disagree	1	2	3	4	5	6	7	8	9 Strongly Agree

The Consent Form was too long.

Strongly Disagree	1	2	3	4	5	6	7	8	9 Strongly Agree

The Consent Form was too short.

Strongly Disagree	1	2	3	4	5	6	7	8	9	Strongly Agree

After reading the Consent Form I would have questions for the researcher to answer before I would decide to participate in this study.

Strongly Disagree	1	2	3	4	5	6	7	8	9	Strongly Agree

Most people will be irritated by the length of the Consent Form.

Strongly Disagree	1	2	3	4	5	6	7	8	9	Strongly Agree

I fully read and understood the Consent Form

Strongly Disagree	1	2	3	4	5	6	7	8	9	Strongly Agree

I think that most people who are asked to be in this study will read the *entire* Consent Form carefully.

Strongly Disagree	1	2	3	4	5	6	7	8	9	Strongly Agree

I think that many people who agree to participate in this study will sign the Consent Form without fully reading it.

Strongly Disagree	1	2	3	4	5	6	7	8	9	Strongly Agree

If you were to rewrite the Consent Form, would it end up being

Much Shorter	1	2	3	4	5	6	7	8	9	Much Longer

THIS NOW COMPLETES THE STUDY. THANK YOU FOR PARTICIPATING

Appendix E: High risk consent form

Patient's Initials .....

UNIVERSITY OF ALBERTA

CONSENT FORM

TITLE: **Muscular Fitness in a University Population.**

PRINCIPAL INVESTIGATOR: Dr. Robert Smith **Telephone:** 492-5265
CO-INVESTIGATORS: Dr. Susan Hoff **Telephone:** 492-3229

Purpose:

You are being invited to participate in a research study conducted jointly by the University of Alberta Hospital and the Department of Psychology. Your decision about whether or not to participate is completely voluntary.

The purpose of this study is to investigate muscular health in a university population. Previous research has indicated post-secondary students may be particularly likely to be at risk for developing muscular weakness. The focus on academics and social activity for post-secondary students often leads to a lack of physical activity. A sedentary lifestyle is associated with various muscular degenerative diseases later in life.

In today's study, researchers are interested in your current muscular condition, and what factors are involved in a student's decision to make physical fitness a regular component of their daily routines.

Procedures:

This study involves 2 phases. The first phase will involve a small donation of muscle tissue using a "muscle punch." The second phase is a short questionnaire on physical activity.

Phase 1.

A muscle biopsy is a surgical procedure in which one or more small pieces of muscle tissue are removed for further microscopic or biochemical examination. The procedure is often used in the diagnosis of a neuromuscular disorder.

There are two types of muscle biopsy: (1) an open biopsy, which involves the removal of a small piece of muscular tissue with sharp scissors; and (2) a needle biopsy (or "muscle punch"), in which a small piece of muscle tissue is collected using a large bore needle. The study you will be participating in today will involve the use of a needle biopsy.

The large bore needle will be inserted into your tricep, and the piece of muscle extracted will be roughly the size of a pea. This procedure will take approximately five minutes.

Phase 2.

You will be asked to respond to a short set of questions regarding your physical activity over the past week. There will be no personally identifying information recorded with any written description or with any questions you will be asked to answer.

Benefits of taking part in the study:

There is no direct benefit to you. Your participation in this study may help in the development of programs to increase awareness of the importance of physical fitness.

Risks of taking part in the study:

A muscle biopsy is generally safe and involves minimal risks.

The risks may include the following:

- Infection – this may include invasion by and multiplication of pathogenic microorganisms at the site of the extraction, which may produce subsequent tissue injury and progress to overt disease through a variety of cellular or toxic mechanisms.
- Pain at the site of the injection – you may experience an unpleasant sensation occurring in varying degrees of severity as a consequence of the muscle biopsy.
- Bleeding of the site – you may lose blood at the site of the extraction.
- Bruising of the area – the procedure may damage the capillaries surrounding the site of the extraction, allowing blood to seep into the surrounding tissue causing a bruise.
- Damage to the muscle tissue or other tissues in the area - the needle may injure the underlying soft tissue of the muscle.
- Damage to the bone - the needle may chip or cause a perforation of the bone

Restrictions:

This study is restricted to healthy adults. If you are taking any medications which may thin blood or prevent blood clotting, you may not participate.

The study doctor will discuss this with you in more detail. Please advise the study doctor if you are taking such medication.

Right to Withdraw:

You may choose not to take part in this study. You are free to withdraw from the study AT ANY TIME and for any reason.

Compensation:

There will be no monetary costs to you for participating in this study

Confidentiality:

Your medical records will indicate your participation in this study. Personal records relating to this study will be kept confidential.

Questions and Concerns About the Study:

You can ask the research staff about the study at any time. If you think you have an injury during the course of the study, you should contact the hospital staff. You will be provided with contact information upon completion of the study.

Signatures. Please sign below to indicate that you have read and understood the nature and purpose of the study. Your signature acknowledges the receipt of a copy of the consent form as well as indicates your willingness to participate in this study.

_____
Name (Printed)

_____ _____
Signature Date

Appendix F: Low risk consent form

Patient's Initials .....

UNIVERSITY OF ALBERTA

CONSENT FORM

TITLE: **Muscular Fitness in a University Population.**

PRINCIPAL INVESTIGATOR:	Dr. Robert Smith	**Telephone:** 492-5265
CO-INVESTIGATORS:	Dr. Susan Hoff	**Telephone:** 492-3229

Purpose:

You are being invited to participate in a research study conducted jointly by the University of Alberta Hospital and the Department of Psychology. Your decision about whether or not to participate is completely voluntary.

The purpose of this study is to investigate muscular health in a university population. Previous research has indicated post-secondary students may be particularly likely to be at risk for developing muscular weakness. The focus on academics and social activity for post-secondary students often leads to a lack of physical activity. A sedentary lifestyle is associated with various muscular degenerative diseases later in life.

In today's study, researchers are interested in your current muscular condition, and what factors are involved in a student's decision to make physical fitness a regular component of their daily routines.

Procedures:

This study involves 2 phases. The first phase will involve a test of muscular health using a hand dynamometer. The second phase is a short questionnaire on physical activity.

Phase 1.

A hand dynamometer can be used to measure grip strength and to perform muscle fatigue studies. The device looks like a small rod and is roughly the size of your hand.

You will be asked to squeeze the dynamometer as hard as you can to test for muscular health. Measurements can be made in Newtons or kilograms force. The hand dynamometer can be used alone or in combination with EMG recordings for detailed studies of muscular activity. In this study, the researchers will not be

taking EMG recordings. The researchers are only interested in measuring your performance on the hand dynamometer.

This procedure will take approximately five minutes.

Phase 2.

You will be asked to respond to a short set of questions regarding your physical activity over the past week. There will be no personally identifying information recorded with any written description or with any questions you will be asked to answer.

Benefits of taking part in the study:

There is no direct benefit to you. Your participation in this study may help in the development of programs to increase awareness of the importance of physical fitness.

Risks of taking part in the study:

Use of a hand dynamometer is safe and involves minimal risks.

The risks include the following:

- Minor hand cramping – this is a sudden, involuntary, muscular contraction causing minor pain in your hands or fingers
- Cramping in the bicep or tricep - this is a sudden, involuntary, muscular contraction causing minor pain in your biceps or triceps
- Shortness of breath during the test – you may have minor difficulty breathing or some discomfort while breathing
- Slight increase in heart rate – you may have an increase in the number of heart beats per minutes.
- Minor finger discomfort. – your fingers may feel uncomfortable.
- Minor finger bruising – there may be minor damage to the capillaries in your fingers, allowing blood to seep into the surrounding tissue causing a bruise.

Restrictions:

This study is restricted to healthy adults. If you are taking any medications which may increase the likelihood of bruising, you may not participate.

The study doctor will discuss this with you in more detail. Please advise the study doctor if you are taking any such medication.

Right to Withdraw:

You may choose not to take part in this study. You are free to withdraw from the study AT ANY TIME and for any reason.

Compensation:

There will be no monetary costs to you for participating in this study and therefore no compensation.

Confidentiality:

Your medical records will indicate your participation in this study. Personal records relating to this study will be kept confidential.

Questions and Concerns About the Study:

You can ask the research staff about the study at any time. If you think you have an injury during the course of the study, you should contact the hospital staff. You will be provided with contact information upon completion of the study.

Signatures. Please sign below to indicate that you have read and understood the nature and purpose of the study. Your signature acknowledges the receipt of a copy of the consent form as well as indicates your willingness to participate in this study.

_____
Name (Printed)

_____ _____
Signature Date