Developing an instrument to measure informed consent comprehension in non-cognitively impaired adults

Laura D. Buccini
University of Wollongong


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Developing an Instrument to Measure Informed Consent Comprehension in Non-Cognitively Impaired Adults

Laura D. Buccini

Thesis submitted for the degree of Doctor of Public Health,
School of Health Sciences, University of Wollongong

15 May 2009
Declaration

I, Laura D. Buccini, declare that this thesis, submitted in fulfilment of the requirements for the award of Doctor of Public Health, in the School of Health Sciences, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institution.

Laura D. Buccini

14 May, 2009
Dedication

This work is dedicated to my family, specifically my father Chuck Buccini, my mother Kathy Buccini who although hasn’t been with us for a while, I’m sure she’s been watching over me, my little sister Nichole Buccini, my precious dogs Montana and Dakota and especially to my wonderful husband Keith Boicey. Thanks to all of you for your support, encouragement and guidance. None of this would have been possible without you. Keith your patience, love, support and technical skills over the last three years has been more then impressive. I’m glad we have shared this journey together, as difficult as it may have been at times.

To my wonderful Aussie friends Liz Deane and Anne Maree Parish: you two are the best friends a girl could ask for. I’m indebted to you both for your eternal encouragement and support. Having met you both was worth all the hardship. It will be difficult to leave you but I know our friendship withstand the distance.
Acknowledgements

I'm grateful to my team of supervisors.

- My primary supervisor, Professor Don Iverson provided assistance with the study design throughout the project as well as constructive and helpful comments on the draft of journal articles and the final thesis. Thank you Don for granting me the opportunity to undertake my doctoral studies with you, for the conception of the project and for your guidance during the project.

- My co-supervisors Associate Professor Peter Caputi and Associate Professor Caroline Jones provided assistance with the study design and invaluable feedback on drafts of journal articles and the final thesis. Thank you Peter for your statistical wisdom and guidance through the psychometric analysis. Not to be forgotten are your motivational speeches which were always entertaining!

I would also like to thank the following persons:

- All my family, especially my husband Keith Boicey who always, despite reluctance, proofread my thesis and provided substantial technological assistance.

- All of my friends for their interest in my research and their support.

- Dr. Hazer and Dr Kremer, the best mentors anyone could ask for. The life lessons I’ve learned from each of you are irreplaceable. I only hope I can be the mentor to others like you both have been to me. Thank you for always believing in me!

- My research participants who generously volunteered their time and energy.
Abstract

Informed consent in human research involves a process of communicating information about a research study so as to promote informed decision-making. Current research suggests, however, that a high proportion of participants do not fully understand what it is they are consenting to when enrolling onto a research study. In other words, for many participants consent to participate in research is not truly informed. Evaluating participants’ comprehension of informed consent information through the use of comprehension tests is one possible method for increasing the likelihood that consent to take part in research is truly informed. This thesis, therefore, comprises a series of both qualitative and quantitative studies that build upon one another culminating in the development of a new instrument that measures potential research participants’ comprehension of informed consent information.

Assessments of readability provide a preliminary indication of document complexity in terms of writing style (word choice, sentence length). Therefore, a small-scale descriptive study, as described in Chapter 2, was conducted: i) to measure the readability of Australian-based clinical trial informed consent documents; and ii) to determine whether national or local ethics committees within Australia have formally established informed consent readability standards. The results of the study revealed that the majority of informed consent documents were written at a reading level appropriate for individuals with some university education thus beyond the reading ability of a majority of Australian adults. Official readability recommendations and/or standards could not be located at the national or local level.

One method of gathering evidence of informed consent comprehension is through the use of comprehension tests. Chapter 3 consists of a systematic review, which identifies and critically evaluates instruments that have been developed to measure clinical trial informed consent comprehension in non-cognitively impaired adults. A total of three instruments were identified. Strengths and limitations of each instrument were evaluated against the following criteria: i) method of item generation; ii) type and
format of test items; iii) administration and interpretation of test results; and iv) psychometric properties.

None of the instruments identified in Chapter 3 were developed based on a construct definition. This may be due to the absence of an accepted construct definition of informed consent comprehension. A construct definition provides a framework for determining how an instrument should be constructed, implemented, interpreted and applied. Furthermore, the validity of what is being measured will rest largely on that definition. Chapter 4 describes and reports on the results of a qualitative study, involving an international expert panel, which was conducted to develop consensus for a construct definition of informed consent comprehension.

The construct definition proposed in Chapter 4 was utilized as the conceptual framework for the development a new of informed consent comprehension instrument, called the Modular Informed Consent Comprehension Assessment (MICCA) instrument. Chapter 5 describes the methodologies used to develop the instrument and presents the results of preliminary readability and content validity testing. Chapter 6 is an extension of Chapter 5 in that it presents the results of a psychometric study conducted to assess the reliability, generalizability and validity of the MICCA. Results of the psychometric study provide preliminary evidence that the MICCA can be utilized in various clinical trial settings and can produce reliable and valid test scores. Evidence of comprehension through the use of comprehension instruments, such as the MICCA, can help ensure that consent to participate in a research study is truly informed.
Publications and Presentations

The following publications and presentation have been produces as a result of the research conducted for this thesis.

Publications in Refereed Journals


Conferences and Presentations


**List of Acronyms and Abbreviations**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>AU</td>
<td>Australia</td>
</tr>
<tr>
<td>BICEP</td>
<td>Brief Informed Consent Evaluation Protocol</td>
</tr>
<tr>
<td>BIQ</td>
<td>Brief Investigator Questionnaire</td>
</tr>
<tr>
<td>CA</td>
<td>Canada</td>
</tr>
<tr>
<td>DICCT</td>
<td>Deaconess Informed Consent Comprehension Test</td>
</tr>
<tr>
<td>Fog</td>
<td>Gunning Fog Index</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HREC</td>
<td>human research ethics committees</td>
</tr>
<tr>
<td>ICC</td>
<td>Intraclass correlation</td>
</tr>
<tr>
<td>MICCA</td>
<td>Modular Informed Consent Comprehension Assessment</td>
</tr>
<tr>
<td>MIMS</td>
<td>Monthly Index of Medical Specialties</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>QuIC</td>
<td>Quality of Informed Consent questionnaire</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SMOG</td>
<td>Simple Measure of Gobbledygook</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>WAIS-R</td>
<td>Wechsler Adult Intelligence Scale-Revised</td>
</tr>
<tr>
<td>WRAT-R</td>
<td>Wide Range Achievement Test-Revised</td>
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</tbody>
</table>
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CHAPTER 1

Introduction

1.1 Informed Consent Comprehension - A Brief Background

The history of medical research is plagued with a number of unethical practices of human experimentation including the Tuskegee syphilis studies, the Nazi medical war crimes of World War II, and the Milgram obedience experiments. Henry Beecher (1966), a well-known physician, wrote a paramount article for the New England Journal of Medicine providing details of 22 clinical trials that knowingly risked the health and lives of study participants. More recently the Kennedy Krieger Institute, affiliated with Johns Hopkins School of Medicine, conducted a study where children were intentionally exposed to hazardous levels of lead paint to determine the effectiveness of varying lead abatement procedures.

The ethical and legal risks associated with research involving human participants have been highlighted recently in a number of lawsuits. Two cases include the widely-publicized research-related deaths of 18-year-old research participant Jesse Gelsinger, who died four days after entering a gene transfer trial at the University of Pennsylvania and Ellen Roche, a healthy volunteer who was asphyxiated after participating in a clinical trial for a proposed asthma treatment at Johns Hopkins University. Both universities were sued for inadequate study protocols related to the protection of research participants. These and many other publicized cases of unethical treatment have resulted in the development and revisions of ethical codes of research conduct and tighter regulations specifically related to informed consent, in a continuing effort to better protect the welfare of research participants.

Informed consent, a mainstay of human research ethics, is primarily guided by the legal and ethical principle of patient autonomy. Patient autonomy refers to the concept that potential research participants must be provided with and comprehend all information necessary to make an informed decision regarding whether or not to participate in a research study. The challenge, however, remains as to whether participants actually comprehend informed consent information. Research suggests that few participants,
when enrolling onto a trial, fully understand what it is they are consenting to.11-15 In other words, for many participants consent to take part in a research study is not truly informed.

Readability formulas have been utilized as an indirect method of measuring comprehension of informed consent documents. Readability refers to the degree in which a person can read and understand written material and is usually expressed as a grade level equivalence i.e., the number of years of formal westernised education generally required to understand a document.16,17 Readability research indicates that most informed consent documents are written above a 12th grade readability level, equivalent to some tertiary (university) education.18-21 This creates a problem, however, as approximately half of the populations in westernised nations have literacy skills at or below an 8th grade reading level.22 It has been suggested that reducing the readability of informed consent documents may increase comprehension, but there is little empirical evidence to support this assumption. In fact, comprehension and readability are not highly correlated constructs.16,23 In reality, assessments of readability provide a preliminary evaluation of the complexity of a document in terms of writing style (e.g. word choice, sentence length) and provide an indication of the likelihood of a person being able to read a document. Readability information, thus, can be used as a guide for writing and revising documents with simpler language.

More recently, informed consent comprehension instruments have been developed as a method of establishing evidence of comprehension. The majority of comprehension instruments have been designed specifically for cognitively impaired adults24-27 (i.e. those with psychiatric or other mental impairments). However, evidence suggests that even participants with no known cognitive impairments can fail to understand informed consent information.28-30 Therefore, it is important that both cognitively and non-cognitively impaired research participants are evaluated for comprehension of informed consent information pertaining to a research study.

A major issue with informed consent comprehension instruments designed for non-cognitively impaired research participants is that they have been developed in the absence of a construct definition. A construct definition provides a framework for
determining how an instrument will be constructed, implemented, interpreted and applied. To date, there is no universally accepted definition for the construct of informed consent comprehension. Conceptually there is a lack of consensus about what should be measured with the major obstacle being how to define comprehension. Without a clear definition we cannot be sure that these instruments actually measure what they purport to measure.

1.2 Thesis Outline

The primary aims of this thesis were: i) to propose a construct definition of informed consent comprehension; and ii) based on the proposed definition, develop an instrument that measures informed consent comprehension. Before proceeding with developing the construct definition and comprehension instrument, some fundamental background studies needed to be conducted. Therefore, this thesis is comprised of a series of qualitative and quantitative studies that build upon one another culminating in the development and psychometric evaluation of an informed consent comprehension instrument.

Results from the first study (Chapter 2), an evaluation of readability, provided an indication of the complexity of a convenience sample of informed consent documents utilized in clinical trial research. This study was followed by a systematic review intended to identify and evaluate instruments currently available for measuring informed consent comprehension in non-cognitively impaired adults (Chapter 3). Given the importance of developing an instrument based on a construct definition, a qualitative study (Chapter 4) was then conducted in effort to develop a standardized construct definition of informed consent comprehension. The construct definition proposed from Chapter 4 was utilized as a framework for developing the informed consent comprehension instrument described in Chapter 5. Chapter 6, an extension of Chapter 5, involves a preliminary psychometric analysis of the informed consent comprehension instrument.

This thesis is presented in the format of journal articles. All chapters have been either submitted or accepted for publication with the exception of Chapter 6, which will be
submitted as a manuscript following thesis submission. The publication status of each study is noted within each corresponding chapter. To minimize repetition throughout the thesis, the first introduction paragraph of each chapter has been slightly adapted from the manuscript version submitted/accepted for publication.

1.3 Significance of the Thesis

Interest in informed consent comprehension has increased with the growth of clinical trial litigations, specifically in the United States (US).\textsuperscript{32} In keeping with US Federal regulations and international standards of Good Clinical Practice, the onus is upon the research investigator to ensure that consent is properly informed.\textsuperscript{8,33} Failure to follow such ethical and legal requirements can result in significant legal action.\textsuperscript{32} Research investigators are urged to invest time and effort into obtaining evidence that consent is truly informed. One method of doing so is through the use of standardized, informed consent comprehension tests.

To date, informed consent comprehension instruments have been developed in the absence of an accepted construct definition of informed consent comprehension.\textsuperscript{34-36} Developing an instrument based on an accepted construct definition would be expected to enhance the validity of the instrument.\textsuperscript{37} Valid informed consent comprehension instruments can, therefore, be used in the research setting to inform clinical decision making. Research investigators can utilize such instruments to identify gaps in participants’ knowledge, providing additional education where necessary, before enrolling participants onto a research study. Without establishing evidence of comprehension, it is difficult to conclude that consent to participate in a research study is based on a truly informed, autonomous decision.
1.4 References


CHAPTER 2
An Australian Based Study on the Readability of HIV/AIDS and Type 2 Diabetes Clinical Trial Informed Consent Documents


2.1 Introduction

2.1.1 Informed Consent
Informed consent documents (patient information sheets and consent forms) are often used to disclose information about research studies. However, participants may have difficulty fully understanding these documents as they tend to be complex and laden with scientific language. The complexity of informed consent documents is further exacerbated by poor literacy skills. Approximately half of the populations in Australia and other western nations have literacy skills at or below an 8th grade level,\(^1\) equivalent to 8 years of formal education (see Table 2.1). Yet, many informed consent documents are written above a 12th grade reading level, equivalent to some tertiary (university) education.\(^2-6\) In other words, there is a large gap between what potential research participants are expected to be able to read and their actual reading ability. To account for low literacy skills of the general population, organisations such as the United States (US) Food and Drug Administration,\(^7\) the US National Cancer Institute\(^8\) and the American Academy of Family Physicians\(^9\) have implemented readability guidelines, recommending informed consent documents be written at or below an 8th grade reading level.

2.1.2 Readability
Readability refers to the degree in which a person can read and understand written material.\(^10\) Readability formulas measure the readability of written prose (text) through mathematical equations based on words per sentence, syllables per word, and/or
familiarity of words. They also assess vocabulary load, the most significant predictor of text difficulty. Readability scores are expressed as grade level equivalence which refers to the number of years of formal westernised education generally required to understand a document. For example, a document that is found to have a 7th grade readability score is expected to be understandable to an individual with at least seven years of formal, western education. The Fry Readability Formula (Fry), Gunning Fog Index (Fog), Flesch Reading Ease, and Simple Measure of Gobbledygook (SMOG) are four formulas commonly used to assess readability of informed consent documents.

Table 2.1: Percent of Populations At or Below an 8th Grade Reading Level

<table>
<thead>
<tr>
<th>Country</th>
<th>Prose % ≤ 8th grade</th>
<th>Document % ≤ 8th grade</th>
<th>Qualitative % ≤ 8th grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>44.1</td>
<td>44.8</td>
<td>43.3</td>
</tr>
<tr>
<td>Canada</td>
<td>43.2</td>
<td>35.1</td>
<td>43.0</td>
</tr>
<tr>
<td>Switzerland</td>
<td>51.3</td>
<td>45.0</td>
<td>37.4</td>
</tr>
<tr>
<td>USA</td>
<td>46.6</td>
<td>49.6</td>
<td>46.3</td>
</tr>
</tbody>
</table>

*The ability to understand and use information from text; The ability to locate and use information in tables, charts, etc; The ability to perform calculations using numbers within printed text.

Readability formulas are not without limitations. They do not measure content, organisation, word order, formatting or imagery. As well, readability should not be mistaken to imply comprehension, as these constructs generally are not highly correlated with one another. Instead assessments of readability can provide a preliminary evaluation of the complexity of a document in terms of writing style (e.g. word choice, sentence length) and gives an indication of the likelihood that an individual will be able to read a document. This information can then be used as a guide to write and revise documents with simpler language. With the implementation of online readability calculators, and those that are built in to word processing programs, reliable readability scores can be calculated easily and efficiently.

Over the past 30 years the majority of the research evaluating the readability of clinical trial informed consent documents has been conducted within the United States. Results of these studies indicate that informed consent documents are often written well above the recommended 8th grade reading level, with most documents requiring a tertiary
Little research on the readability of clinical trial informed consent documents has been conducted in the Australian context. Therefore, the primary aims of this study were to: i) measure the readability of a convenience sample of Australian-based HIV/AIDS and type 2 diabetes 2004-2006 clinical trial informed consent documents and ii) examine whether readability guidelines for informed consent documents exist within Australia at the national and/or local level. Ethics approval for this study was granted by the University of Wollongong, Human Research Ethics Committee.

2.2 Methods

2.2.1 Readability Assessments

Readability analyses were conducted on a convenience sample of informed consent documents provided by an HIV/AIDS research center and a type 2 diabetes research center located in New South Wales, Australia. Principal investigators from each center granted us access to informed consent documents of clinical trials conducted between January 2004 and January 2006. Informed consent documents were included in the readability analysis based on the following selection criteria: i) they originated from clinical trials that involved adult participants (≥18 years of age), ii) they originated from phase III treatment clinical trials that had been approved by an Australian human research ethics committee, and iii) they did not originate from the same sponsoring organization (in order to obtain a diverse sample of documents). The final sample included 10 informed consent documents, 5 from each research center.

Each informed consent document consisted of: i) a patient information sheet (also referred to as a plain language statement), which usually is a lengthy document that provides a detailed description of the clinical trial, and ii) a consent form, typically a one-page summary of the details presented in the patient information sheet. Patient information sheets and consent forms were assessed separately for readability using the SMOG and Fog readability formulas. These two formulas were selected because they correlate highly with one another (r=0.96), can easily be calculated manually (by hand) or with a free online readability calculator, and can calculate readability up to a grade 18 reading level.20 As well, psychometric studies indicate the SMOG and Fog are
reliable and valid methods for analysing readability of health-based literature\textsuperscript{21-23} and they are commonly utilised within Australia.\textsuperscript{24-16}

To ensure reliability, readability scores were calculated manually and then by online readability calculators. See Table 2.2 for a description of the procedures required to conduct the manual calculations. Unlike the manual methods, online readability calculators have the ability to quickly calculate the readability of the full text document, which otherwise is not practical. Mean readability scores for each patient information sheet and consent form were calculated based on the average of the four readability calculations: i) the online Fog,\textsuperscript{27} ii) the manual Fog,\textsuperscript{28} iii) the online SMOG,\textsuperscript{29} and iv) the manual SMOG.\textsuperscript{30} An independent samples t-test was conducted to determine whether there were significant differences in readability scores between HIV and type 2 diabetes informed consent documents, and between patient information sheets and consent forms.

<table>
<thead>
<tr>
<th>Table 2.2: Readability Hand Calculation Methodology</th>
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<tr>
<td></td>
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<tr>
<td><strong>Formula</strong></td>
</tr>
<tr>
<td>SMOG\textsuperscript{30}</td>
</tr>
<tr>
<td>Add 3 to the square root of the total number of polysyllabic words (3+ syllables) from a 30 sentence sample.</td>
</tr>
<tr>
<td>FOG\textsuperscript{28}</td>
</tr>
<tr>
<td>Multiply 0.04 by the (average sentence length + % of words 3+ syllables) from a 100 word sample.</td>
</tr>
<tr>
<td><strong>Document Sample</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>SMOG\textsuperscript{30}</td>
</tr>
<tr>
<td>The 30 sentence sample consisted of ten consecutive sentences chosen from the beginning, middle and end of the document.</td>
</tr>
<tr>
<td>FOG\textsuperscript{28}</td>
</tr>
<tr>
<td>100 word sample randomly chosen from a continuous passage within the consent documents with at least one hundred words.</td>
</tr>
</tbody>
</table>

2.2.2 Readability Standards

In Australia, the National Health and Medical Research Council (NHMRC) is responsible for developing guidelines for the conduct of human research. These guidelines are then implemented by local human research ethics committees (HRECs), who are accountable for reviewing research proposals involving human participants. We reviewed publicly available regulatory and policy documents from the NHMRC and the two local ethics committees who had previously approved the informed consent
documents under study. These documents were examined to determine whether readability guidelines for informed consent documents had been established by these organisations. The NHMRC and the two local ethics committees were contacted via e-mail correspondence to identify whether they utilised any informal readability standards or “rules of thumb” that may not have been mentioned within the published documents.

2.3 Results

2.3.1 Readability Assessments

The following mean readability scores are reported in terms of grade level equivalence (i.e. the number of years of formal western education required to read a particular document. The mean ± SD for the five HIV/AIDS patient information sheets and five consent forms was 14.0 ± 0.54 and 14.28 ± 2.84 respectively. The mean ± SD for the five type 2 diabetes patient information sheets and the five consent forms were 13.01 ± 1.01 and 12.93 ± 1.90. The mean ± SD for all patient information sheets was 13.5 ± 0.93 and for all consent forms were 13.61 ± 2.38.

Figures 2.1 and 2.2 graphically compare the mean readability scores of the informed consent documents to the 8th grade readability guidelines established by U.S organizations.\textsuperscript{7,9} None of the forms were readable at or below the 8th grade reading level. Participants would be required to have at least some tertiary education to read 9 out of 10 patient information sheets and 8 out of 10 consent forms. There was no significant difference (p>.05) in readability scores between the HIV/AIDS and the type 2 diabetes informed consent documents or between the patient information sheets and the consent forms (p>.05).
Figure 2.1: Mean Readability Scores of HIV/AIDS Informed Consent Documents

Figure 2.2: Mean Readability Scores of Type 2 Diabetes Informed Consent Documents
2.3.1 Readability Standards

Formal readability guidelines could not be located upon examination of the NHMRC’s most recent revisions to the National Statement of Ethical Conduct in Human Research. E-mail correspondence with the NHMRC confirmed that while formal guidelines have not been established at the national level, each individual human research ethics committee has the freedom to set their own readability policies/guidelines. Formal readability guidelines or policy statements also could not be located upon review of the two local human research ethics committees’ regulatory and policy documents. However, e-mail correspondence with the two ethics committees revealed that both use informal rules to assess the readability of informed consent documents. Through discussions, committee members subjectively determine whether informed consent documents are appropriate for the intended study population. Documents perceived as exceeding the study population’s reading ability may be sent back to researchers for revisions.

2.4 Discussion

The findings from this study suggest that high readability levels of clinical trial informed consent documents are not unique to United States. Australian based HIV/AIDS and type 2 diabetes informed consent documents analysed in this study were, on average, written at a grade 13 reading level. In other words, an individual would require a minimum of 13 years of formal western education (i.e. some tertiary education) to be able to read the informed consent documents. We do not know the reading skill level of patients who participated in these clinical trials. However, since almost half of Australians have reading skills at or below an 8th grade reading level, it is probable that many Australians would find this sample of informed consent documents difficult to read.

Some studies have suggested that a positive relationship exists between readability and the length of a document. In the sample of informed consent documents used in this study, there was no significant difference in readability grade levels between the multi-paged patient information sheets and single page consent forms. However, consent forms that were heavily loaded with polysyllabic vocabulary (>3 syllables) and
long compound sentences resulted in higher readability scores than the corresponding patient information sheets. For example, to read the multi-page patient information sheet from Form 1 of the HIV/AIDS documents would require approximately 13 years of formal westernised education. By comparison, 16 years of formal westernised education would be required to read the shorter one-page consent form (see Figure 2.1).

While there is an absence of national readability standards, the two local human research ethics committees contacted for this study did recognise the importance of evaluating the readability of informed consent documents. However, subjective readability assessments may be ineffective as informed consent documents that underwent subjective evaluation by the local research ethics committees on average required a university education. One problem with conducting subjective evaluations may be that those who serve on ethics committees often hold higher-level degrees (Master’s and/or Doctorate degrees) thus, tend to read and write at a grade 15 level or higher. Therefore, it may be difficult for ethics committee members to identify documents that are actually written at an 8th grade reading level.

This study should be of concern to human research ethics committees whose responsibility it is to ensure that the welfare of potential research participants is protected. Unreadable informed consent documents may result in patients rejecting trial participation altogether or conversely may result in their participating in a trial with inadequate consent. Although readability in and of itself does not ensure comprehension, it does provide a preliminary assessment of a document’s complexity. Therefore, a necessary first step toward reducing the complexity of informed consent documents is to implement formal readability policies/standards into the human research ethics application and review process.

As part of the research ethics application process it is recommended that Australian human research ethics committees set a standard requiring all informed consent documents to be written at or below an 8th grade readability level, unless a research investigator can provide appropriate justification that this requirement is unnecessary. Moreover, research investigators should be required to measure and declare on the ethics application the readability grade level of their study’s informed consent
documents. For compliance purposes an ethics committee administrator could conduct random readability assessments to validate the readability levels stated on an investigator’s ethics application. Informed consent documents that do not meet the 8th grade readability standards should be returned to investigators for revision. Readability can be calculated quickly online or through software packages, requiring little additional time or resources on behalf of the ethics committee and the investigator. Formal assessments of readability should, therefore, be considered a routine step in the research ethics application and review process.

Readability is an indirect method utilized for measuring understanding of informed consent documents. A more direct method of assessing comprehension of informed consent information is through the use of informed consent comprehension tests. The following chapter (Chapter 3) reviews and evaluates tests that have been developed to measure informed consent comprehension specifically in non-cognitively impaired adults.
2.5 References


CHAPTER 3
Assessing Clinical Trial Informed Consent Comprehension in Non-Cognitively Impaired Adults: A Systematic Review of Instruments


3.1 Introduction
Informed consent in human research requires that potential research participants are provided with and comprehend all information necessary to make an informed decision about whether or not to participate in a research study.1-4 Empirical studies have explored the relationship between participants’ comprehension and informed consent. Although participants often report understanding informed consent documents, when assessed for comprehension utilizing non-standardized5-8 and standardized5,9,10 comprehension tests, few can state the purpose of the trial or specific aspects of trial procedures.

Readability formulas have been utilized as an indirect method of measuring comprehension of informed consent documents. More recently, informed consent comprehension tests have been developed as a direct method of establishing evidence of participants’ comprehension of informed consent information. Comprehension tests are often developed in the form of true/false, multiple choice or open-ended questionnaires and are most effective at assessing recall of information.11 Formal tests of comprehension are commonly utilized with potential research participants who are at an increased risk for lacking the capacity to consent12 (e.g. psychiatric disorders). Standardized instruments have been developed specifically for this population.13-16 Although psychiatric disorders are a risk factor for poor understanding, studies comparing comprehension of patients with and without psychiatric illnesses have shown that the presence of a psychiatric disorder does not predict whether or not participants...
can understand informed consent information. In other words, even participants with no known psychiatric disorders fail to understand informed consent information. Therefore, cognitively impaired and non-cognitively impaired potential research participants should be evaluated for comprehension especially when enrolling onto greater than minimal risk trials. The purpose of this review was to identify, critically review and compare existing standardized instruments that measure clinical trial informed consent comprehension in non-cognitively impaired adults.

3.2 Methods

Two researchers independently conducted the literature search to increase consistency and accuracy of the search and selection process. Literature searches were carried out on PubMed (Medline), PsycInfo, CINHAL, ScienceDirect, ERIC, and Cochrane Library for English language articles published between January 1980 and September 2008 that described the development of standardized instruments that measure clinical trial informed consent comprehension in non-cognitively impaired adults. The following search terms were used: informed consent, understanding, comprehension, assessment, instrument, test, questionnaire and survey. In addition, reference lists of all potentially relevant publications were reviewed (see Figure 3.1).

A total of 275 publications were identified (see Figure 3.1). Instruments selected for review included those that were: objective measures of comprehension, designed for clinical trial research, developed for non-cognitively impaired adults, and included formal psychometric evaluations. Instruments were excluded if they focused on consent onto pediatric trials, the construct under study was primarily capacity or competency, or the instrument was developed specifically for psychiatric or cognitively impaired populations. Consent in each of these alternative contexts requires additional considerations, which are not included in this paper. Each instrument selected for review was critically evaluated based on the following characteristics: i) method of item generation; ii) type and format of test items; iii) administration and interpretation of test results; and iv) psychometric properties.
Figure 3.1 Systematic Review Search Strategy

Total publications identified; 
\( n = 275 \)

Studies identified through database searches; 
\( n = 269 \)

Duplicates removed; 
\( n = 21 \)

Studies screened; 
\( n = 248 \)

Excluded studies; \( n = 236 \)
- Not relevant; \( n = 132 \)
- Not original research; \( n = 8 \)
- Non-standardized assessments; 
  \( n = 38 \)
- Assessment of satisfaction of consent process; \( n = 6 \)
- Assessment of capacity/competency to consent; \( n = 13 \)
- Readability assessment of consent documents; \( n = 7 \)
- Assessment of health literacy; \( n = 5 \)
- Subjective assessment of understanding; \( n = 6 \)
- Assessment for psychiatric/cognitively impaired; \( n = 13 \)
- Assessment of pediatric/proxy consent; \( n = 8 \)

Potentially relevant studies retrieved for further evaluation; 
\( n = 12 \)

Studies identified through reference lists; \( n = 6 \)

Total potentially relevant publications reviewed; 
\( n = 18 \)

Excluded studies; \( n = 15 \)
- Assessment of capacity/competency to consent; \( n = 5 \)
- Subjective assessment of understanding; \( n = 3 \)
- Not original research; \( n = 2 \)
- Assessment for psychiatric/cognitively impaired; \( n = 3 \)
- Assessed pediatric or proxy consent; 
  \( n = 2 \)

Studies included in final systematic review; 
\( n = 3 \)
3.3 Results

Three instruments met the defined inclusion criteria: the Deaconess Informed Consent Comprehension Test (DICCT),\textsuperscript{20} the Quality of Informed Consent (QuIC)\textsuperscript{9} questionnaire and the Brief Informed Consent Evaluation Protocol (BICEP).\textsuperscript{21} Comprehension, utilizing these instruments, was measured by providing potential research participants with information about a clinical trial, in the form of informed consent documents, followed by a series of questions that potential participants were required to answer before consent was permitted. The BICEP was an exception to this process; the comprehension assessment was conducted after consent to participate had been given. A brief description of each instrument is summarized in Table 3.1.

| Table 3.1 Summary of Informed Consent Comprehension Instruments |
|---|---|---|
| **Time** | DICCT: <10 min | QuIC: <10 min | BICEP: <10 min |
| **Domain** | Objective understanding of antiinfective clinical trials | Objective & subjective understanding of phase I, II or III cancer clinical trials | Satisfaction with the quality of the consent process & assessment of common therapeutic misconceptions |
| **Format** | 14 item open-ended structured interview questions | Section A: 20 objective statements with 3 point response scale (disagree, unsure, agree). Section B: 14 subjective likert items | 12 item structured open-ended interview questions |
| **Item Generation** | Based on U.S federal consent requirements | Based on U.S federal consent requirements and published empirical literature | Based on published empirical literature on consent and advice from advisory group |
| **Scoring** | Ranges from 0-28; higher scores = greater comprehension | Summary score (objective + subjective items) ranges from 0-100; higher scores = greater comprehension | Subjective items: 0-10; Therapeutic misconceptions questions: 0-5; higher scores = greater comprehension |
| **Validity** | Criterion related: WAIS-R: \( r = 0.44 \); WRAT-R: \( r = 0.33 \) | Content Validity: based on consultation with expert panel | Face Validity (no details) |
| **Reliability** | Inter-rater \( r = 0.84 \) | Test-retest: Form A: ICC=0.66; Form B: ICC=0.77 | Inter-rater: ICC=0.75 |
3.3.1 Item generation and Format

There is variation in terms of how the informed consent comprehension instruments have been developed and the content they measure. The DICCT and the QuIC questionnaire were developed to assess research participants’ comprehension of the consent requirements stipulated by United States (US) Federal Regulations4 (see Table 3.2). Both instruments include at least one objective test item for each consent requirement. The QuIC questionnaire contains additional objective and subjective test items. The added objective items measure understanding of difficult clinical trial concepts as noted in empirical research studies such as: placebo, therapeutic misconception, and blinding.9 The subjective items evaluate how well participants feel they understand the clinical trial. The BICEP also contains both objective and subjective measures. Objective items specifically measure participants’ therapeutic misconceptions, which has been previously defined as false attributions (misunderstandings) of clinical trial research.22 The subjective test items, on the other hand, aim to assess participants’ general satisfaction with the informed consent process.21

Table 3.2: United States Consent Requirements4

<table>
<thead>
<tr>
<th>US Core Consent Requirements</th>
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<tbody>
<tr>
<td>1. A statement that study involves research</td>
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<tr>
<td></td>
</tr>
<tr>
<td>2. Description of foreseeable risks/discomforts</td>
</tr>
<tr>
<td>3. Description of potential benefits</td>
</tr>
<tr>
<td>4. Alternative treatment/procedures in lieu of participation</td>
</tr>
<tr>
<td>5. Description of how confidentiality of records will be maintained</td>
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<tr>
<td>6. For research involving greater then min. risk</td>
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<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>7. A statement that participation is voluntary</td>
</tr>
<tr>
<td>8. Contact info if have questions, comments, complaints about the study</td>
</tr>
</tbody>
</table>
The depth of comprehension assessed by each instrument also varies. The objective section of the QuIC questionnaire consists of statements about the clinical trial; participants are asked to indicate whether they agreed/disagreed with each statement. Generally, agree/disagree response options are best suited to assess lower level processing of factual information but are less desirable when tapping deeper levels of comprehension.\textsuperscript{23,24} The open-ended interview structure of the DICCT and the BICEP may offer greater flexibility for assessing the depth and breadth of comprehension. This gain in flexibility, however, may be offset by loss of standardization across test administrators. To increase standardization, a series of structured prompting questions, utilized by test administrators to extract detailed responses from participants, was incorporated into the BICEP.

### 3.3.2 Test Administration

Participant recruitment is one of the most costly and time consuming functions of clinical trial research.\textsuperscript{25} Therefore, the likelihood of an investigator utilizing a comprehension assessment during the patient recruitment process will be greatly influenced by the ease of test administration. The QuIC questionnaire is a multiple-choice (agree/disagree) assessment that requires approximately ten minutes to complete. Since it is self-administered by participants, little burden is placed on the investigator. Unfortunately, this self-administration process provides little opportunity for follow-up, feedback or education regarding participants’ incorrect responses or misconceptions.

Both the DICCT and the BICEP contain open-ended interview questions. The DICCT requires little or no training to administer and score the test items, and can be completed in less than ten minutes. The BICEP also takes less than 10 minutes to administer. However, participants’ responses to the BICEP need to be individually coded which may increase the total time spent during the testing process.

### 3.3.3 Interpretation of Test Results

The authors of each of the instruments indicate that higher test scores equate to greater comprehension of informed consent information.\textsuperscript{9,20,21} Little additional interpretive guidance beyond this is provided. For example, is there a minimal acceptable level of comprehension that must be reached, and is this level the same for all clinical trials?
Should results from the comprehension assessments be used as inclusion/exclusion criteria for enrolment onto a clinical trial or simply for educational purposes? This additional interpretive information could prove useful when determining how to interpret a potential research participant’s comprehension score.

### 3.3.4 Psychometrics

Adequate reliability was established for all instruments. The inter-rater reliability of the DICCT was based on comprehension scores of the first 50 participants who enrolled onto an ambulatory trial. Two investigators scored the tests independently. The inter-rater reliability of the DICCT was $r = 0.84$, satisfying the minimum reliability standards for clinical decision-making. For the BICEP, three raters independently scored 42 clinical trial participants’ responses to the comprehension assessment. The inter-rater reliability of raters’ scores were moderately correlated (Intraclass correlation [ICC] = 0.75). To establish test-retest reliability of the QuIC questionnaire, two copies of the full instrument were sent to a random sample of patients enrolled onto a cancer clinical trial. Respondents completed the second copy of the instrument, on average, 15.4 days after completing the first. Test retest reliability was determined to be of moderate level; ICC = 0.66 - 0.77.

While the three instruments were not formally evaluated for generalizability, all were developed to be utilized across a variety of clinical trials involving different diseases/conditions. The DICCT contains specific questions related to the use of medications. Therefore this instrument may not be appropriate for other types of trials such as prevention trials, diagnostic trials, screening trials or quality-of-life trials. The QuIC questionnaire was developed specifically for cancer clinical trials (Phases I-III) and includes cancer specific language. The authors note that further studies need to be conducted to establish generalizability to other non-cancer trials. Because of the open-ended nature of the BICEP and the absence of trial specific questions, it appears to generalize well across a range of clinical trials.

Validity was formally evaluated for both the DICCT and the QuIC questionnaire. Miller and colleagues correlated the DICCT scores to the vocabulary subtest of the revised Wechsler Adult Intelligence Scale (WAIS-R) and the reading subtest of the Wide Range
Achievement Test (WRAT-R) in effort to establish concurrent validity. The DICCT was moderately correlated with both the WAIS-R (r = 0.44) and the WRAT-R (r = 0.38). This overlap in test performance was interpreted as indicating that the DICCT was moderately effective in measuring comprehension. The QuIC questionnaire established content validity through the use of an expert panel. Three bioethicists reviewed the test items and made suggestions with regard to clarity, emphasis and framing of the items. Expert consensus was established for all but one item, which was subsequently deleted from the final questionnaire. Validity was not formally determined for the BICEP. The authors suggest that face validity was established, although it is not clear who was included in that assessment or what benchmark criteria were used during the assessment process.

3.4 Discussion

We identified three instruments that purport to measure clinical trial informed consent comprehension in non-cognitively impaired adults. These comprehension instruments attempt to provide the evidence to make judgments about whether, and to what extent, comprehension of clinical trial information actually occurs amongst potential research participants. Each instrument has its own strengths and weaknesses which should be considered when selecting an instrument for use during the clinical trial recruitment process. Identifying the most appropriate instrument primarily depends on the type of trial being conducted and resources allocated for test administration.

As previously stated, the comprehension instruments may be limited in their usability across various clinical trials. For example, the QuIC questionnaire was designed specifically for cancer clinical trials and includes cancer-specific language. Therefore, as is, this instrument may be inappropriate for non-cancer trials. Furthermore, the QuIC questionnaire and the DICCT were developed based on US consent requirements (see Table 3.2) and may require significant adaptation to correspond with another country’s consent requirements.

Given that participant recruitment is one of the most costly functions of the clinical trial process it is also important to consider the amount of resources that can be allocated to test administration. Although all instruments take less than ten minutes to complete,
each has different administrative requirements. For example, the BICEP is more
demanding in terms of coding and scoring responses compared to the self-administered
QuIC questionnaire.

A current challenge of incorporating comprehension tests into the clinical trial
recruitment process relates to the interpretation of test scores. Important steps in the
instrument development process include determining relevant assessment domains and
how test scores will be interpreted. The three identified instruments provide little
direction on how potential research participants’ test results should be interpreted and
subsequently used during the clinical trial recruitment process. Thus the development of
guidelines could assist physicians and clinical trial researchers understand how to use
individual test results to guide clinical decision-making. Furthermore, additional
psychometric evaluation may be warranted to establish criterion-referenced scoring as
opposed to norm-referenced scoring. Norm reference scoring yields an estimate of the
position of the tested individual in a predefined population and refers to the process of
comparing one test-taker’s score to the scores of his or her peers. Criterion-referenced
scoring, on the other hand, translates test scores into a statement about the
understanding expected of a person with that score or their relationship to a specified
subject matter. Criterion-referenced scoring would therefore provide a defensible
standard for determining when a minimal level of comprehension has been achieved.

Standardized measures of comprehension should enhance the likelihood of obtaining
meaningful consent. Physicians and clinical researchers can utilize such instruments to
identify gaps in potential research participants’ knowledge and provide additional
education where necessary. Moreover, informed consent is grounded in the ethical
principle of respect for a person’s autonomy. Thus, to treat potential research
participants as autonomous agents, it is imperative to ensure understanding of the
consent information has actually occurred enabling them to make autonomous decisions
about participation.

Further work related to the development of standardized instruments should consider
the strengths and limitations of currently available instruments. As well, research should
aim to better define the construct of informed consent comprehension. A well defined
construct definition can provide a standardized framework for determining how an instrument should be constructed thus may minimize the variability that currently exists between instruments. Therefore, Chapter 4 describes an international study dedicated to developing a construct definition of informed consent comprehension.
3.5 References


CHAPTER 4
Towards a Construct Definition of Informed Consent Comprehension


4.1 Introduction
Informed consent comprehension tests have been developed to provide much-needed evidence to make judgments about whether adequate comprehension of informed consent information occurs among potential research participants. Despite widespread agreement about the need to obtain evidence of comprehension, uncertainty remains about how to establish that evidence. Amongst the informed consent comprehension tests currently available for non-cognitively impaired adults,\textsuperscript{1-3} there is large variation in how they have been developed, the domain of content which they measure and how to utilize test results to guide clinical trial decision making. The variation between comprehension tests may be due to the absence of a standardized, agreed upon definition of the construct of informed consent comprehension. Developing a construct definition can provide a standardized framework for determining how an instrument should be constructed, implemented, interpreted and applied.\textsuperscript{4}

To date, there are no systematic efforts to define the construct of informed consent comprehension. Therefore, our aim was to conduct an international study to establish consensus on a preliminary working definition. This chapter proposes a preliminary construct definition of informed consent comprehension. It is anticipated that our proposed definition will stimulate further investigation in order to create a theoretical and conceptual basis for instrument development. The study received ethics approval from the University of Wollongong Human Research Ethics Committee.
4.2 Methods

4.2.1 Participants
A convenience sample of 19 international experts, 5 from the United States (US), 7 from Canada (CA) and 7 from Australia (AU), agreed to take part in our study. The panel was derived from a list of individuals with 5 or more years of research and/or applied work experience in the discipline of human clinical trial research (n=11), human research ethics (n=4) or education/cognition (n=4). Many of the panelists had extensive experience in two or more of the disciplines listed above.

4.2.2 Phase 1 - Preliminary Construct Definition
The first step toward the development of a construct definition was to propose an initial definition to the international expert panel. This definition acted as a baseline from which subsequent definitions emerged. The initial definition was developed by examining the following three commonly debated issues related to measuring informed consent comprehension: i) What specific consent information should participants comprehend? ii) What does it mean to comprehend? and iii) How should it be determined that comprehension of the consent information has occurred? We drew on three primary sources of information to formulate answers to these questions, namely: i) definitions and ethical requirements established by human research regulatory agencies from the United States,5,6 Australia,7 Canada8 and the International Conference on Harmonization-Good Clinical Practice;9 (GCP) ii) lessons learned from previous research studies conducted on informed consent comprehension;10-15 and iii) the information processing theory of comprehension.16-19

4.2.3 Phases 2 – 5: Revisions Based on Experts’ Responses
We utilized the Delphi consensus approach to gather knowledge, opinions and eventually consensus for a definition of the construct of informed consent comprehension.20 Experts were asked to respond to the preliminary definition by responding to the following open-ended statements: i) The elements of the proposed definition that I did not like include; ii) I feel the following elements are essential to keep in the proposed definition; and iii) My suggestions for modifying or changing the definition are as follows. Expert responses were e-mailed to the primary researcher who
acted as the facilitator of the Delphi consensus process. The facilitator de-identified expert responses in order to maintain experts' anonymity. Responses were then summarized and thematically analyzed. Themes that consistently arose across one-third or more of the experts were used to revise the definition. Experts were given two weeks to respond to each revision. A reminder email was sent to all experts one week before the deadline. This process of collecting, summarizing and thematically analyzing expert responses was repeated until consensus of a construct definition was reached (see Figure 4.1). Experts who were unable to provide a response by the indicated deadline were not included in subsequent revisions.

Figure 4.1 Delphi Consensus Approach Methodology-Communication Flow Diagram

Phase 1: Preliminary Construct Definition
A preliminary definition was proposed and sent to experts via email

Phase 2: First Revision
Revisions made based on expert feedback to the preliminary definition (Phase 1)

Phase 3: Second Revision
Revisions made based on expert feedback to the first definition (Phase 2)

Phase 4: Third Revision
Revisions made based on expert feedback to the second definition (Phase 3)

Phase 5: Consensus
The first author called for consensus based on expert feedback to the third revision (Phase 4)
4.3 Results

4.3.1 Phase 1: Initial Construct Definition

Using the data gathered from our three primary information sources, we formulated answers to the commonly debated questions (see Table 4.1). These answers provided a basis for the initial construct definition which was formulated as follows:

*Informed consent comprehension takes place once there is evidence that a potential participant has integrated the information determined to be most influential to his or her decision to participate in a study which is confirmed through recall.*

Table 4.1 Answers to Commonly Debated Questions

<table>
<thead>
<tr>
<th>Answers To Commonly Debated Questions</th>
<th>Resources Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>What specific consent information should participants comprehend?</td>
<td>1) Information that should be understood includes the subset of all disclosed</td>
</tr>
<tr>
<td></td>
<td>information that is most influential to a potential research participant’s decision to</td>
</tr>
<tr>
<td></td>
<td>take part in a research study.</td>
</tr>
<tr>
<td></td>
<td>US^5^, AU^7^, CA^8^, GCP^9^ &amp; lessons learned from previous studies^1^-^3^,^10^-^15^</td>
</tr>
<tr>
<td>What does it mean to comprehend?</td>
<td>Comprehension refers to the integration of previous knowledge with novel information</td>
</tr>
<tr>
<td></td>
<td>presented within consent documents of which can then be recalled from memory.</td>
</tr>
<tr>
<td></td>
<td>Information processing theory of comprehension^16^-^19^</td>
</tr>
<tr>
<td>How is it determined that comprehension has occurred?</td>
<td>Research indicates that a sign consent form alone is not synonymous with comprehension.</td>
</tr>
<tr>
<td></td>
<td>Therefore, we need to establish methods that extract evidence of comprehension. According to the information processing theory, comprehension can be extracted by assessing recall of the integrated information (previous knowledge with novel information).</td>
</tr>
<tr>
<td></td>
<td>Information processing theory of comprehension^16^-^19^ &amp; lessons learned from previous studies^1^-^3^,^10^-^15^</td>
</tr>
</tbody>
</table>

4.3.2 Phase 2 - First Revision

All 19 experts responded to the initial definition: 5 from the US, 7 from CA, and 7 from AU (see Table 4.2-Phase 1). Experts indicated that the terminology “most influential” was too subjective and should be replaced with a more objective standard such as national or international consent regulations. Experts also wanted clarification regarding exactly what information was to be “integrated.”
To clarify the concept of “integration” we referred to the information processing theory of comprehension which states that comprehension is a product of the integration of prior knowledge with novel (new) information. Integration of novel information is an important component of comprehension. Instruments that do not attempt to measure understanding of novel information may be measuring a construct other than that of comprehension. For example, many informed consent comprehension tests currently available contain generic question items in order to enhance the usability of the instrument across a variety of trials. Yet, participants who have general knowledge of clinical trials or have previously participated in a clinical trial could correctly complete the comprehension test without truly understanding specific information about the trial to which they intend to enroll. These instruments, therefore, may in fact be measures of general knowledge rather than comprehension. It is the integration of both prior knowledge with novel information that is fundamental to the process of comprehension.16-19

Based on experts’ comments and suggestions, the first revised definition was proposed as follows:

Informed consent comprehension can be said to occur when there is evidence that a potential participant has integrated novel consent information with his/her current knowledge which at a minimum, includes the set of information determined by national and international ethics regulations to be most important for potential participants to understand when deciding whether to take part in a research study.
### Table 4.2 Expert Feedback

<table>
<thead>
<tr>
<th>PHASE 1 - BASED ON PRELIMINARY DEFINITION</th>
<th>Experts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems with this definition:</td>
<td></td>
</tr>
<tr>
<td>The terminology ‘influential information’</td>
<td>18/19 (95%)</td>
</tr>
<tr>
<td>Dislike ‘through recall’ as evidence of understanding could be obtained through other methods</td>
<td>15/20 (75%)</td>
</tr>
<tr>
<td>Restructure the definition (wording)</td>
<td>8/19 (42%)</td>
</tr>
<tr>
<td>Identify components essential to keep:</td>
<td></td>
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<tr>
<td>The requirement of comprehension</td>
<td>19/19 (100%)</td>
</tr>
<tr>
<td>Integration of information</td>
<td>18/19 (95%)</td>
</tr>
<tr>
<td>Evidence of comprehension</td>
<td>16/19 (84%)</td>
</tr>
<tr>
<td>Suggestions for changes:</td>
<td></td>
</tr>
<tr>
<td>Influential information: Change to important, necessary or salient</td>
<td>17/19 (90%)</td>
</tr>
<tr>
<td>Define who determines that this information is most important or influential (i.e. ethics regulations)</td>
<td>13/19 (69%)</td>
</tr>
<tr>
<td>Take out ‘confirmed through recall’</td>
<td>7/19 (37%)</td>
</tr>
<tr>
<td>Structure of definition (wording): Change ‘informed consent comprehension takes place’ to ‘informed consent comprehension can be said to occur’</td>
<td>7/19 (37%)</td>
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<table>
<thead>
<tr>
<th>PHASE 2 - BASED ON FIRST REVISION</th>
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<tbody>
<tr>
<td>Problems with this definition:</td>
<td></td>
</tr>
<tr>
<td>The word ‘novel’</td>
<td>12/16 (75%)</td>
</tr>
<tr>
<td>Definition is long and may be confusing</td>
<td>9/16 (56%)</td>
</tr>
<tr>
<td>Regulations that are most important is ambiguous</td>
<td>9/16 (56%)</td>
</tr>
<tr>
<td>Identify components essential to keep:</td>
<td></td>
</tr>
<tr>
<td>Evidence</td>
<td>16/16 (100%)</td>
</tr>
<tr>
<td>Integration</td>
<td>16/16 (100%)</td>
</tr>
<tr>
<td>National and international ethics regulations</td>
<td>15/16 (94%)</td>
</tr>
<tr>
<td>Evidence established ‘at the time when deciding whether or not to take part’</td>
<td>10/16 (60%)</td>
</tr>
<tr>
<td>Suggestions for changes:</td>
<td></td>
</tr>
<tr>
<td>Take out the word novel</td>
<td>12/16 (75%)</td>
</tr>
<tr>
<td>Further explain the set of information that participants should understand (i.e. consent requirements)</td>
<td>7/16 (43%)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>PHASE 3 - BASED ON SECOND REVISION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems with this definition:</td>
<td></td>
</tr>
<tr>
<td>Length of definition: too wordy, becomes confusing</td>
<td>12/15 (80%)</td>
</tr>
<tr>
<td>Identify components essential to keep:</td>
<td></td>
</tr>
<tr>
<td>Evidence</td>
<td>15/15 (100%)</td>
</tr>
<tr>
<td>Integration</td>
<td>14/15 (93%)</td>
</tr>
<tr>
<td>Who determines: national and international ethics regulations</td>
<td>14/15 (93%)</td>
</tr>
<tr>
<td>Definition of when the evidence should be established: i.e. ‘at the time when deciding whether or not to take part’</td>
<td>12/15 (80%)</td>
</tr>
<tr>
<td>Suggestions for changes:</td>
<td></td>
</tr>
<tr>
<td>Break the definition down into separate sentences to make it easier to understand</td>
<td>9/15 (60%)</td>
</tr>
<tr>
<td>Structure the definition as criteria based using bullets points</td>
<td>6/15 (40%)</td>
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</table>

<table>
<thead>
<tr>
<th>PHASE 4 - BASED ON THIRD REVISION</th>
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</thead>
<tbody>
<tr>
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<td></td>
</tr>
<tr>
<td>None</td>
<td>14/14 (100%)</td>
</tr>
<tr>
<td>Identify components essential to keep:</td>
<td></td>
</tr>
<tr>
<td>Evidence</td>
<td>14/14 (100%)</td>
</tr>
<tr>
<td>Integration</td>
<td>14/14 (100%)</td>
</tr>
<tr>
<td>Who determines: national and international ethics regulations</td>
<td>14/14 (100%)</td>
</tr>
<tr>
<td>Evidence should be established ‘at the time when deciding whether or not to take part’</td>
<td>12/14 (86%)</td>
</tr>
<tr>
<td>Bullet points</td>
<td></td>
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<tr>
<td>Suggestions for changes:</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>14/14 (100%)</td>
</tr>
</tbody>
</table>
4.3.3 Phase 3 - Second Revision

Sixteen experts (84%) responded to the first revision: 3 from the US, 7 from CA and 6 from AU (see Table 4.2-Phase 2). Twelve of these experts (75%) stated they felt the word “novel” was awkward and suggested it be removed. As well, it was suggested that “national and international regulations” was not sufficiently specific and should be changed to “national and international consent requirements”.

Based on experts’ comments and suggestions, the second revised definition was proposed as follows:

*Informed consent comprehension can be said to occur when there is evidence, established when the potential participant decides whether or not to take part in the research study, that his/her current knowledge has been integrated with the consent information which at a minimum includes the consent requirements stipulated by national and international ethics regulations.*

4.3.4 Phase 4 - Third Revision

Fifteen of the previous sixteen experts (94%) responded to the second revision of the definition: 3 from the US, 6 from CA, and 6 from AU (see Table 4.2-Phase 3). Overall, the experts stated that they were satisfied with the content of the definition. However, there was consistent feedback pertaining to the length and structure of the definition. Suggestions were provided on how to breakdown the definition by using bullet points. Based on experts’ comments and suggestions, the third revised definition was proposed as follows:

*Informed consent comprehension can be said to occur when the following conditions are met:*

- There is evidence that a potential participant has integrated his/her current knowledge with the consent information;
- The evidence occurs at the time the potential participant decides whether or not to take part in the research study;
- At a minimum, the integrated consent information includes the consent requirements stipulated by national and international ethics regulations.
4.3.5 Phase 5 - Call for Consensus

Fourteen of the fifteen experts responded to the third revision of the definition: 3 from the US, 6 from CA, and 5 from AU (see Table 4.2-Phase 4). Experts continued to express satisfaction with the content and structural changes. With no new suggestions for revisions, the primary researcher of this study called for consensus on the third revision of the construct definition. All 14 experts approved the third revision.

4.4 Discussion

The importance of developing a standardized definition of any construct, such as informed consent comprehension, cannot be over stated as the validity of what is being measured will rest largely on the definition. As well, standardization allows for comparison of results across research and enhances generalizability of findings. Developing a standard method of communicating about informed consent comprehension could have a significant impact on how comprehension is measured and how subsequent instruments are developed.

Our study began with a convenience sample of 19 experts. Five experts did not respond by the predefined deadlines and therefore were categorized as dropouts. We did not seek explanation from non-respondents regarding why they did not comment on the definition. Although our study included international representation, the number of experts was relatively small and only represented three countries that are culturally similar. To account for these study limitations, further development of the construct definition should involve a larger global panel of experts from more culturally diverse countries. This process could greatly enhance the strength and generalizability of the definition.

Utilizing the Delphi approach provided a systematic method for establishing consensus on a preliminary definition. However, this approach is limited in that it does not provide an avenue for stimulating in-depth discussion or debate nor does it require experts to provide justification for their responses to the open-ended statements. Modifications to the definition were, therefore, based on the level of agreement between experts. Feedback that was not thematically similar across 1/3 or more of the expert panel was not used in the construct revisions. Therefore, significant input may have
been dismissed because it did not meet our predefined cut-offs. In order to develop a strong argument that supports the construct definition, additional studies should employ methods that require experts to justify their suggestions to modify the definition. Furthermore, the generalizability of the construct definition may be limited due to the small sample of experts and the narrow geographic and cultural representation of those experts.

With the growing legal and ethical concerns about informed consent, more rigorous research in this area is warranted. While acknowledging that there are several study limitations, this study should be considered as an initial step toward standardization of a construct definition of informed consent comprehension. It is our hope that this proposed definition will stimulate further investigation and theoretical development to enhance understanding of the construct and hence, help guide the development of informed consent comprehension instruments.

An appropriate next step should be to collect additional data through empirical research studies. Such studies should include a larger number of experts from diverse geographic and cultural backgrounds. The experts ought to be representative of a variety of disciplines such as those involved in human research, research ethics, cognitive sciences and law. The immediate focus of the discussions would be further refinement of the preliminary construct definition of informed consent comprehension. Other issues that should be addressed during the forum include: i) Are current national and international regulations appropriate as they stand or do they need to be revised? ii) Which research participants should be required to undergo a comprehension evaluation? iii) How much comprehension should be required? This platform would encourage those who are responsible for the ethical conduct of research to engage in dialogue about how these and other related issues might be approached in their own countries and in international collaborative research.

In its current state, our proposed definition includes the requirement that potential participants understand information stipulated by national and international consent requirements. There are a number of consent requirements that exist within and between
countries, which can vary greatly in content. This is an important an issue for multi-center, international trials where it may not be practical for participants to comprehend each country’s separate requirements. Perhaps it would be possible to establish a standardized, core set of consent requirements that are applicable within and across countries. Discussion is also needed regarding whether the various consent requirements, as they stand, represent what they were intended to represent or whether they in fact need to be revised.

Other immediate issues relate to whether all research participants should be evaluated for comprehension and what type of evaluations should be utilized. Such decisions will most likely be based on the level of risk presented in a study. For example, should informed consent comprehension be assessed only for greater than minimal risk research and if so, is there a universal, agreed upon definition for greater than minimal risk studies? Should the amount of evidence of comprehension that is required directly correspond to the level of risk involved with a study? Should evaluations be oral or written and does the type of evaluation depend on the literacy level/skills of the intended population (i.e low versus high literacy)? Answers to these questions are very important, primarily because they inform test developers about the type of test items that should be included within a comprehension test. As well, they inform clinical trial researchers of when comprehension should be assessed and how much comprehension is enough to conclude consent to participate is truly informed.

Although there are instruments that have been developed to measure informed consent comprehension they have been developed in the absence of a construct definition.1-3 To our knowledge this is the first standardized proposed definition. This research should, therefore, be viewed as a preliminary study; additional research is required to improve the proposed definition and address the many unanswered questions that remain. It is intended that this definition, upon further development, can be used to guide the development of new instruments designed to measure comprehension of informed consent information. As described in Chapter 5, the construct definition of informed consent comprehension presented in this chapter (Chapter 4) is subsequently used to develop a new instrument that measures informed consent comprehension specifically for non-cognitively impaired adults.
4.5 References

CHAPTER 5

A New Measure of Informed Consent Comprehension: Part I – Instrument Development


5.1 Introduction

Two basic approaches characterize the development of informed consent comprehension test developed for non-cognitively impaired adults: generic instrument development and trial specific instrument development.\(^1\)\(^-\)\(^3\) Generic instruments are those that include test items that are broadly applicable across a variety of different clinical trials (e.g. participation is voluntary, participants can withdraw at anytime). Although generic instruments have the ability to assess general knowledge about clinical trial research they may fail to measure participants’ actual understanding of a particular clinical trial. Conversely, trial specific instruments are designed to measure factual understanding of design characteristics and research protocols of a particular clinical trial (e.g. side effects, procedures, etc) and may be most appropriate if the objective is to measure ‘true’ informed consent. However, due to the specificity of test items, the utilization of trial specific instruments may be limited to the clinical trial for which they were designed.

Developing an instrument that is trial specific as well as usable across various clinical trials is quite challenging given the variability that exists between trials in terms of design characteristics and research protocols. Web-based applications represent potentially powerful and effective tools for developing such an instrument. A web-based application can automate the process of creating trial specific question items that are relevant to a particular clinical trial, resulting in an instrument that can be utilize in different clinical trial settings yet specific to a particular trial.
Currently, there is no gold standard for measuring comprehension of informed consent. This may be due to the absence of a standardized construct definition of informed consent comprehension. A construct definition provides a framework for determining how an instrument will be constructed, implemented, interpreted and applied. Furthermore, the validity of what is being measured will rest largely on that definition.

Given the lack of a universally accepted construct definition, Buccini et al. conducted an international study to establish a preliminary working definition for the construct of informed consent comprehension. The study consisted of an expert panel (N=19) from the United States, Australia and Canada to gather knowledge, opinions and eventually consensus for a definition. The outcome of this study was the proposal of the following definition:

*Informed consent comprehension can be said to occur when the following conditions are met:*

- There is evidence that a potential participant has integrated his/her current knowledge with the consent information;
- The evidence occurs at the time the potential participant decides whether or not to take part in the research study;
- At a minimum, the integrated consent information includes the consent requirements stipulated by national and international ethics regulations.

The aim of this study was, therefore, to develop a new measure of informed consent comprehension with four primarily goals in mind: 1) to utilize the newly proposed construct definition as a framework for developing a standardized instrument specifically for non-cognitively impaired adults, 2) to ensure the instrument measures comprehension of clinical trial information by including trial specific test items, 3) to design the instrument in a web-based format to enhance utilization across diverse clinical trials, and 4) to ensure administration and respondent burden are minimal for research investigators and research participants.

Two instruments were developed, the Brief Investigator Questionnaire (BIQ) and the Modular Informed Consent Comprehension Assessment (MICCA). The MICCA is the
core instrument designed to measure comprehension of informed consent information. The BIQ was developed as a companion instrument that functions to create trial specific test items within the MICCA that are customized to reflect the design characteristics and research protocols of clinical trials. Both instruments were developed as web-based applications providing flexibility to construct a comprehension test that is specific to a particular clinical trial yet can be utilized across a variety of trials that focus on different diseases/conditions. The purpose of this chapter is, therefore, to describe the methodologies used to develop the instruments and present the results of preliminary readability and content validity testing of the MICCA.

5.2 Methods
We followed the phases of test development described by Downing and Haladyna. The phase defines the conceptual framework, followed by test construction and revisions of the test items, and ends with an evaluation of the instrument in terms of reliability and validity. Each phase is described below.

5.2.1 Phase 1: MICCA Conceptual Framework
The construct definition of informed consent comprehension proposed by Buccini et al provided a framework for developing the MICCA. Specifically, we utilized the definition as a guide to define the instrument’s content domain and determine how the content domain will be measured.

A critical first step in instrument development is establishing the content domain that the instrument wills measure. The content domain specifies the realm of information that will be tested by the instrument. According to the construct definition our instrument should measure comprehension of “the consent requirements stipulated by national and international ethics regulations”. We further defined this domain to include national and international informed consent disclosure requirements. As a starting point, we included the requirements set out by the United States, Canada, Australia, and International Standards of Good Clinical Practice. In addition, we chose to include in the content domain commonly held misconceptions about clinical trials, as cited by empirical research (see Appendix A). For example, few clinical trial participants understand such terms as randomization and double-blind study.
We then determined that the content domain would be measured through a combination of the generic and the trial specific test items. The construct definition states informed consent comprehension occurs when “there is evidence that a potential participant has integrated his/her current knowledge with the consent information.” Generic test items would function to assess current (background) knowledge, and trial specific test items would measure understanding of specific aspects unique to each clinical trial.

5.2.2 Phase 2: MICCA Test Construction
Once the framework was constructed, we began the second phase of instrument development, establishing the construction methodology. During this phase, the primary tasks were to: i) determine the structure and format of the instrument, and ii) write and revise test items and corresponding response options.

The likelihood of a research investigator utilizing a comprehension assessment during the patient recruitment process is influenced by the ease and efficiency of test administration. Therefore, we developed test items using multiple-choice formats. Not only are multiple choice tests easy to administer, they are also effective at assessing understanding of concepts (i.e. paraphrasing, definitions, examples or concepts) and principles (statement of relationship between two or more concepts). Furthermore, multiple-choice items are easy for the test taker to complete, for the test administrators to score, and convert well from a pencil-and-paper format to a web-based format.

Test items and response options were developed using one of three multiple choice formats. A description and justification for using each format is described below:

True/False (T/F) Statements are best at assessing understanding of information that requires lower level processing. True/False statements were, therefore, developed to assess understanding of items within our content domain that was general knowledge or factual information about clinical trial research. An ‘I don’t know’ response option was included in an effort to minimize guessing by participants.

Standard multiple choice questions (MC) are effective at assessing understanding of concepts or principles where only one correct answer is available. We incorporated MC
questions for items within our content domain that require understanding of more complex information then that assessed by True/False statements (i.e. such as the relationship between multiple concepts). The MC response options included a correct answer, two distractors and an ‘I don’t know’ option. Research suggests that more than two distractors does little to improve test score statistics and often results in inappropriate distracters.\textsuperscript{19,20}

Multiple answers, multiple choice questions (Checkboxes) assess the same level of understanding as the single answer MC questions.\textsuperscript{6,18} However, we utilized the checkbox format when there was more than one possible correct answer. Five answer options were generated which included: between two and three correct answer options, between one and two distracter answer options and an ‘I don’t know’ answer option.

To minimize administration and respondent burden, one multiple-choice test item was generated for each item within our content domain. The final sample of multiple-choice test items consisted of a core set of generic items and a subset of trial specific items. All test items were integrated into an interactive web-based application. The web-based application proves flexibility to create trial specific test items that are customized for a particular clinical trial.

5.2.3 Phase 3: BIQ Survey Construction
The development of trial specific test items requires detailed information pertaining to the design characteristics and research protocols associated with a clinical trial. Therefore, the Brief Investigator Questionnaire (BIQ) was developed as a tool to extract specific clinical trial information. That information is then used to create the trial specific test items that appeared on the MICCA. To operate in conjunction with the MICCA, the BIQ was also developed as a web-based application. It is a questionnaire that is completed online by a research investigator. Responses to BIQ questions automatically generate a customized, web-based version of the MICCA which includes a core set of generic test items and a variable subset of trial specific test items a.
BIQ question items were developed to correspond to the trial specific test item on the MICCAa. Response options to the BIQ questions were structured in a predefined format to reduce respondent errors and enhance uniformity of responses. The pre-defined responses were developed based on clinical trial protocols commonly cited in the Australian New Zealand Clinical Trials Registry21 and in the Monthly Index of Medical Specialties (MIMS).22 For example, the most common side effects reported in the MIMS were used to develop the predefined list of side effects. However, due to extensive variations in clinical trial protocols it was impossible to create a comprehensive list of responses. Therefore, three free-text cells were integrated into the response list to allow investigators to add protocols not already provided (see Appendix C).

5.2.4 Phase 4: Revisions
Three experts with experience working in clinical trial research were asked to review and evaluate the full web-based version of the MICCA (i.e. all possible test items) and the BIQ. The MICCA was also reviewed by a convenience sample of eleven lay participants. Specifically, experts and lay participants were asked to comment on the clarity and structure of each test items, response options and test instructions. The final version of the MICCA and BIQ reflect the feedback obtained from the experts and lay participants.

5.2.5 Phase 5: Preliminary Testing

5.2.5.1 Readability of the MICCA
We used simple, plain language when formatting test items, response options and test instructions. The goal was to keep the readability of the instrument at or below an 8th grade reading level, as recommended by the United States Food and Drug Administration,7 the United States National Cancer Institute23 and American Academy of Family Physicians.24 The MICCA should therefore, be readable to those with at least 8 years of formal Western education. We measured readability of the full online version of the MICCA using the Simple Measure of Gobbledygook (SMOG)25 and the Gunning Fog Index (Fog)26 readability formulae. Psychometric studies indicate that these two formulae are reliable and valid methods for analysing readability of health-based literature.27-30

aTo generate the MICCA, a research investigator completes the online BIQ questions which relate to the specific details of his/her trial. Once those responses are submitted they feed into another web based application which generates a version of the MICCA that includes trial specific questions based on responses to the BIQ and generic questions which are standardised across all versions of the MICCA.
5.2.5.2 Content Validity of the MICCA

Four clinical trialists who had no previous involvement with this study were asked to review the MICCA for content validity. Each trialist was provided with the list of items that represent the content domain (see Appendix A) and given access to the full web-based version of the MICCA. The experts were asked to identify and comment on whether at least one test item had been developed for each item in our content domain.

5.3 Results

5.3.1 MICCA Test Construction and Revisions

We originally developed a 24-item modular web-based instrument, the Modular Informed Consent Comprehension Assessment (MICCA). The MICCA included 14 true/false statements, 4 multiple-choice questions, and 6 checkbox questions. Of these 24 test items, 12 were generic and 12 trial specific. Minor edits to instructions, test items and response options were offered by experts and lay participants. Among the expert panel there was consensus to add a question that assesses whether participants understand what it means to sign a consent form. This question was formatted as a generic multiple-choice test items and integrated into the MICCA. The final full version of the MICCA includes a total of 25 test questions: 14 true/false, 5 multiple-choice and 6 Checkboxes. Of these 25 test items, 13 were generic and 12 trial specific (see Appendix B).

5.3.2 BIQ Test Construction and Revisions

The BIQ consists of 10 questions corresponding to one or more of the trial specific test items on the MICCA. The three experts who reviewed the BIQ suggested minor changes to the wording of question items. They also provided specific recommendations for including additional response options to the predefined lists. For example, two experts suggested adding ‘long-term health care follow-up’ as a response option to question eight which pertains to the benefits of trial participation. As well, all three experts suggested listing ‘hours’ as an additional response option related to the duration of trial participation (question ten). The final version of the BIQ is inclusive of the experts’ feedback (see Appendix C).
5.3.3 Preliminary Testing- Readability and Content Validity

Assessments of both readability and content validity were carried out using the full web-based version of the MICCA (inclusive of all 25 questions). The readability assessment using the SMOG\textsuperscript{25} and Fog\textsuperscript{26} readability formulas indicated that the full instrument is readable at a 5.5 grade (SMOG) and 6 grade (Fog) reading level, well below our targeted grade 8 reading level.

There was 100\% agreement from the four clinical trialists who independently reviewed the instrument that one test item had been appropriately developed for each item within our content domain. The exception to this was with regard to ‘blinding of a trial’. All reviewers identified that two questions related to ‘blinding’. Since two forms of blinding commonly arise in clinical trials, it was the intent during instrument development to generate one separate test item for double-blinding and one for single-blinding.

5.4 Discussion

The MICCA is the first informed consent comprehension instrument to be developed based on an explicitly stated construct definition of informed consent comprehension. Instruments developed in the absence of such a definition are likely to lack construct and/or content validity which, in turn, would result in the appropriateness of the instrument being challenged.\textsuperscript{4} In line with the construct definition proposed by Bucchi et al.\textsuperscript{5} the MICCA measures comprehension by incorporating both generic and trial specific approaches of instrument development. Generic test items functioned to assess current (background) knowledge about clinical trial research while trial specific test items assess consent information specific to a clinical trial.

Developing an instrument that is trial specific as well as usable across a variety of clinical trials presents a fundamental challenge, specifically given the variability that exists between clinical trials in terms of trial design and research protocols. Therefore, unique to our methodology was the development of the MICCA and the BIQ. Both web applications work in union to generate a version of the MICCA which includes customized, trial specific test items; a method intended to enhance the usability of the MICCA across clinical trials.
The MICCA was developed to assess comprehension related to the informed consent disclosure requirements from the United States, Canada, and Australia which may enhance the utilization of the instrument internationally. The MICCA was not designed, however, to address important disclosure requirements as stipulated by other countries. Therefore, as it stands, the MICCA may not be an applicable measure of comprehension in clinical trials conducted outside of the United States, Canada and Australia. This limitation, however, presents an opportunity for further research. The MICCA could be further developed to account for additional informed consent disclosure requirements not already specified.

An assessment of construct validly by four clinical trialists provides preliminary evidence that the MICCA measures the construct of informed consent comprehension as defined by Buccini et al. Yet, to establish whether the MICCA can be utilized to inform clinical decision making, additional psychometric testing is required. Therefore, in a follow-up study we will conduct an international study to assess the psychometric properties of the MICCA. Specifically, we will evaluate the MICCA for reliability, generalizability and validity. The results of the psychometric evaluation will provide further information about the degree to which the MICCA test items measure the construct of informed consent comprehension.

It is also recommended that additional readability assessments are conducted. The findings of our initial assessment indicate that the MICCA is readable to persons with a minimum of a grade 6 education (i.e. 6 years of formal westernized education). However, only the full, 25-item instrument was assessed. Since the MICCA can result in various combinations of test items, it is suggested that the readability of the different versions of the MICCA are assessed in the future.

This chapter presents a comprehensive methodology for constructing two instruments that function in tandem to measure research participants’ comprehension of informed consent information. The MICCA holds promise as an instrument that can be utilized across a range of trials to assess comprehension in terms of general knowledge about clinical research and specific aspects about a particular clinical trial. Evidence of comprehension through the use of comprehension tests, such as the MICCA, can help
ensure consent to participate is in fact informed. The following Chapter (Chapter 6) describes the results of a study conducted to evaluate the psychometric properties of the MICCA.
5.5 References


CHAPTER 6

A New Measure of Informed Consent Comprehension:
Part II – Preliminary Psychometric Evaluation

This chapter will be submitted for publication to the journal Contemporary Clinical Trials.

6.1 Introduction

The Modular Informed Consent Comprehension Assessment (MICCA) is a recently developed instrument that purports to measure comprehension of informed consent information.\(^1\) The aim of comprehension tests, such as the MICCA, is to establish evidence that participants’ consent to take part in a research study is truly informed. Although other comprehension instruments are available,\(^2\)-\(^4\) the MICCA is the first to our knowledge to be developed based on a consensus construct definition of informed consent comprehension. A construct definition gives meaning to an abstract concept and provides direction as to how that concept should be measured.\(^5\) Moreover, the validity of the instrument will largely be determined by its construct definition.\(^6\)

The development of the MICCA was based on the construct definition of informed consent comprehension proposed by Buccini et al.\(^7\) This definition specifies the realm of information that should be measured by comprehension instruments (i.e., content domain) and how test items should be constructed. Accordingly, the content domain should include, at a minimum, “rational and international informed consent disclosure requirements.”\(^7\) The authors of the MICCA defined the content domain as the informed consent disclosure requirements as stipulated by the United States,\(^8\)-\(^9\) Australia,\(^10\) Canada\(^11\) and International Standards of Good Clinical Practice\(^12\) as well as commonly held misconceptions about clinical trial research as cited by empirical research\(^13\)-\(^18\) (e.g. randomization, placebo) (see Appendix A).

The MICCA was developed using a combination of generic and trial specific test items.\(^1\) This approach was utilized to satisfy the criteria of the construct definition,
which states that informed consent comprehension is the product of integrating current knowledge with informed consent information. Generic items were included in the MICCA to assess current (i.e., background) knowledge. Items in the content domain that were broadly applicable to all clinical trials were generated as generic test items (e.g., participation is voluntary, participants are free to withdraw). Trial specific items were included to measure issues within the content domain that related to the specific design characteristics and research protocol of a designated clinical trial (e.g., side effects, benefits, procedures). Of the 25 test items that comprise the MICCA, 13 items were developed as generic items and 12 items as being trial specific (see Appendix B).

A preliminary assessment of MICCA’s content validity by four clinical trialists indicated that the MICCA test items were representative of the desired content domain. However, to determine whether the MICCA satisfies the construct definition of informed consent comprehension requires more formal psychometric evaluation. Therefore, this chapter describes and reports the outcomes of the first study conducted to assess the reliability, generalizability and validity properties of the MICCA.

Evidence of reliability was considered established if the test items were internally consistent, that is, they explained the majority of the variation in the construct measurement error. Generalizability of the MICCA was assessed by comparing test performance on the MICCA across different types of clinical trials. The trial specific test items included in the MICCA are customized to reflect the design characteristics and research protocol of a particular clinical trial. Therefore, it was hypothesized that participants’ overall performance on the MICCA and performance based on question type (i.e. generic and trial specific test items) would be similar across different clinical trial conditions. These results could, therefore, provide evidence that the MICCA can be utilized in different clinical trial settings and protocols.

Validity was assessed using the known-group approach where a priori hypotheses were generated about the relationship between test performances for groups known to differ on the variable being measured. According to Buccini et al informed consent comprehension is the product of integrating background knowledge with the informed consent information. Based on this definition, comprehension should not be attainable.
for those who are not exposed to clinical trial information specific to a clinical trial. Therefore, known-group validity was measured in this study by comparing MICCA test performance scores between participants who received clinical trial information (i.e., informed consent documents) and those who did not. It was hypothesized that test scores would discriminate between participants with and without access to such information. More specifically, it was hypothesized that: i) participants exposed to clinical trial information would perform significantly better across all test performance scores (i.e., overall, generic and trial specific) than those not exposed to clinical trial information; and ii) participants without exposure to clinical trial information would perform better on generic (background knowledge) test items than on trial specific test items.

Comprehension research suggests that background knowledge related to particular subject matter is enhanced through formal education.\textsuperscript{20-22} Therefore, we hypothesized that participants with higher education attainment would have a greater level of background knowledge related to clinical trial research. Since generic test items were developed to assess background knowledge, it was hypothesized that participants with higher education attainment would perform better on generic test items than those with lower education attainment. Although other factors such as personal or family experience with and illness are potential confounders, this information was not gathered at this stage of the study.

6.2 Methods

6.2.1 Study Design
The study incorporated a 5 x 2 factorial design. The research variables explored were level of information, and type of clinical trial. Two levels of information were explored: consent form (information) and title page (no information). Participants in the consent form conditions received an informed consent document describing the details of a particular clinical trial. Participants in the title page conditions received only the title page of an informed consent document; the only information provided on the title page was the de-identified name of the clinical trial.
Five types of clinical trials were examined: cancer, diabetes, hypertension, exercise, and nutrition. These five clinical trials provided diversity in terms of trial purpose (prevention, treatment, lifestyle etc) and disease/condition (illness which intervention is being studied). Such diversity can offer insight into how usable this instrument might be across different types of clinical trials. Furthermore, the informed consent documents for the five clinical trials were publically available and therefore represented real clinical trials, which is methodologically preferable compared to developing “mock clinical trials”.

Participants were first randomly assigned to one of the five clinical trial types and then received either the consent form or the title page associated with that clinical trial, resulting in total of 10 testing conditions. For example, participants assigned to the diabetes-consent form condition received the diabetes clinical trial informed consent document whereas those assigned to the diabetes-title page condition received only the title page of the diabetes informed consent document. All participants, including title page group, completed a Modular Informed Consent Comprehension Assessment (MICCA) that corresponded to his/her assigned clinical trial condition. Participants’ overall performance on the MICCA as well as performance based on question type (i.e., generic versus trial specific) was evaluated and compared within and between conditions.

6.2.2 Participants
To participate in this study, the following inclusion criteria had to be met: i) participants had to be 40 years of age or older (in order to be representative of those who participate in the type of clinical trials selected for this study); and ii) participants had to have access to a computer and the internet as each study component was completed through a secure website.

An international sample of 223 adults, 40 years of age or older took part in the online study. The majority of participants resided in the United States (41.7%). The sample was highly educated with 30% having completed an undergraduate degree and almost 20% a graduate degree. Just over fifteen percent of the participants had ever taken part
in a clinical trial; 4.5% reported not knowing whether or not they had ever participated in a clinical trial. Socio-demographic information of participants is present in Table 6.1.

6.2.3 Informed Consent Documents and MICCA’s
Participants were tested for comprehension of informed consent information using publically available informed consent documents. These documents were based on actual clinical trials conducted between January 2004 and January 2008. To evaluate whether the MICCA could be utilized with different types of clinical trials a diverse sample of clinical trial informed consent documents was selected that related to five types of trials: cancer, diabetes, hypertension, exercise, and nutrition. The selected trial documents varied in terms of disease state, research protocols and design characteristics (see Table 6.2). Each informed consent document consisted of: i) a patient information sheet (i.e. plain language statement) which is the lengthy document providing a detailed description of the clinical trial; and ii) a consent form which is a one-page summary of the details presented in the patient information sheet.

All documents were de-identified by replacing identifying information (e.g. research centre, physician’s name, sponsoring organization’s name, drug names, etc) with generic information (e.g. Dr. John Smith). The content of the informed consent documents was not altered however, the formatting and structure of the informed consent documents was modified. Specifically, the informed consent documents were formatted the same in terms of font, layout, and line spacing, to ensure that the design of the inform consent documents did influence how participants responded to the MICCA test items. A MICCA was generated for each of the five selected informed consent documents. All informed consent documents, title pages and corresponding MICCAs were integrated into a secure interactive web application (see Appendices D-H).
Table 6.1: Socio-demographic Variables

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
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<td></td>
</tr>
<tr>
<td>40-49</td>
<td>73</td>
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<td>50-59</td>
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<td>≥60</td>
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<td>35.0</td>
</tr>
<tr>
<td>Gender</td>
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<td></td>
</tr>
<tr>
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<td>111</td>
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<tr>
<td>Female</td>
<td>112</td>
<td>50.2</td>
</tr>
<tr>
<td>Country</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>69</td>
<td>31.0</td>
</tr>
<tr>
<td>Canada</td>
<td>50</td>
<td>22.4</td>
</tr>
<tr>
<td>United States</td>
<td>93</td>
<td>41.7</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>4.9</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; University</td>
<td>110</td>
<td>49.3</td>
</tr>
<tr>
<td>≥ University</td>
<td>113</td>
<td>50.7</td>
</tr>
<tr>
<td>Previous Clinical Trial Participation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35</td>
<td>15.7</td>
</tr>
<tr>
<td>No</td>
<td>178</td>
<td>79.8</td>
</tr>
<tr>
<td>I don’t know</td>
<td>10</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Table 6.2 Design Characteristics of Clinical Trial Informed Consent Documents

<table>
<thead>
<tr>
<th>Clinical Trial Conditions</th>
<th>Placebo</th>
<th>Randomized</th>
<th>Experimental Procedures</th>
<th>Single-Blinding</th>
<th>Double-Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Exercise</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
6.2.4 Scoring the MICCA

Test items on the MICCA were given a score of 1 for correct responses and 0 for incorrect responses. Questions 20-25 are multiple-choice, multiple response items thus each item may have more than one correct response (see Appendix B). These items were marked correct (given a score of 1) only when all possible correct responses were selected. In other words, partial credit was not awarded for partially correct responses.

An overall test performance score and two performance sub-scale scores (i.e., generic and trial specific), were calculated. The overall test performance score was calculated based on the total number of test items correct across all test items. The generic performance score was calculated based on the number of generic test items correct while the trial specific performance score was calculated based on the total number of trial specific test items correct. Higher scores on the MICCA indicate higher levels of comprehension.

6.2.5 Procedures

As previously described in Chapter 5, the MICCA was developed as a web application therefore, all testing procedures were conducted over the internet. Conducting the study over the internet had the added benefit of being able to recruit an international sample of participants. An initial recruitment email requesting participation for the study was sent to a convenience sample of individuals residing in the United States, Australia and Canada. Further circulation of the recruitment e-mail was requested resulting in the creation of a chain distribution. Electronic consent was obtained from persons who volunteered to participate in the study.

A logic framework programmed into the MICCA web application assigned participants to one of the 10 testing conditions; assignment was determined by the participants’ month of birth. Using a secure web application, participants were presented with the clinical trial informed consent document or the title page which corresponded to their assigned clinical trial condition. Participants were informed they could not print the informed consent documents from their computer, and once they exited away from the study web page, they could not go back. These conditions were adopted to restrict participants from answering test questions by skimming the document for key words.
Skimming, although appropriate for identifying specific pieces of information, is not an effective technique when comprehension of an entire document is the objective.\textsuperscript{23} Once exiting the informed consent document or title page, all participants were automatically directed to a separate web page that contained the version of the MICCA that corresponded to their assigned clinical trial condition. Participants completed the study upon submitting their answers to the MICCA.

Uptake of an instrument into practice is influenced, in part, by the level of administrative and respondent burden.\textsuperscript{24} Therefore, to measure respondent burden we recorded the amount of time it took for participants to complete the MICCA. The web application was programmed to calculate the time it took for participants to complete the MICCA based on the time participants were redirected to the MICCA web page to the time they submitted their answers. Ethics approval for this study was granted by the University of Wollongong Human Research Ethics Committee.

6.2.6 Statistical Analysis

6.2.6.1 Reliability

Internal consistency, using Cronbach’s coefficient alpha, of test items was assessed for each of the clinical trial and information level conditions. Due to low variability in participants’ responses within testing conditions, it was not possible to separately evaluate the internal consistency of generic and trial specific test items. Therefore reliability was measured globally across all test items. Alpha values greater than or equal to .70 were considered to reflect sufficient reliability.\textsuperscript{25}

6.2.6.2 Generalizability

Test performance scores (i.e., overall, generic and trial specific) were converted to Z-scores to allow for comparisons across testing conditions. Analysis of variance (ANOVA) procedures were used to compare mean performance scores across information and clinical trial conditions. This analysis was conducted to determine the extent to which the MICCA was generalizable, and therefore able to be utilized in different types of clinical trials.
6.2.6.3 Validity

The known group approach was conducted to evaluate the validity of the MICCA. Analysis of variance (ANOVA) procedures were utilized to compare mean performance scores (converted to Z-scores) across information conditions (consent form versus title page). If a resulting F-test was significant, analysis of simple main effects (adjusted using a Bonferroni correction) were performed. Secondary analyses were conducted for socio-demographic effects specifically related to education. Participants’ education attainment was dichotomized into those with less than a university education or greater than or equal to a university education. For descriptive and comparison purposes, secondary analyses using Pearson’s correlation coefficients were computed to describe the relationship between test performance scores (i.e., overall, generic and trial specific) and information conditions. Because the study was descriptive and exploratory, the \textit{a priori} significance level was set at 0.05. Data were analysed using SPSS version 15.0.\textsuperscript{26}

6.3 Results

6.3.1 Descriptive Statistics

Mean and standard deviations were calculated for standardised test performance scores (i.e., overall, generic and trial specific) separated by testing conditions (see Table 6.3). Across the five different clinical trial types, the overall standardised test performance scores (mean ± SD) were higher for participants in the consent form conditions (0.89 ± 0.55) compared to those in the title page conditions (-0.82 ± 0.49). Generic and trial specific standardised performance scores were also greater for participants in the consent form conditions (0.57 ± 0.55 and 0.95 ± 0.57 respectively) relative to participants in the title page conditions (-0.52 ± 1.0 and -0.85 ± 0.20 respectively). In the title page conditions, participants scored higher on generic test items (-0.52 ± 1.0) than trial specific items -0.85 ± 0.20). Conversely, in the information conditions, generic scores (0.57 ± 0.55) were lower than trial specific scores (0.95 ± 0.57).
Table 6.3 Mean and Standard Deviations of Standardised Test Scores by Type of Clinical Trial

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Overall</th>
<th>Generic</th>
<th>Trial Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer Clinical Trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent form</td>
<td>24</td>
<td>.92 (.55)</td>
<td>.69 (.46)</td>
<td>.97 (.61)</td>
</tr>
<tr>
<td>Title Page</td>
<td>28</td>
<td>-.79 (.49)</td>
<td>-.59 (.96)</td>
<td>-.83 (.15)</td>
</tr>
<tr>
<td><strong>Diabetes Clinical Trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent form</td>
<td>23</td>
<td>.85 (.61)</td>
<td>.57 (.71)</td>
<td>.90 (.56)</td>
</tr>
<tr>
<td>Title Page</td>
<td>23</td>
<td>-.85 (.42)</td>
<td>-.57 (.92)</td>
<td>-.90 (.19)</td>
</tr>
<tr>
<td><strong>Exercise Clinical Trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent form</td>
<td>20</td>
<td>.93 (.48)</td>
<td>.52 (.56)</td>
<td>1.03 (.42)</td>
</tr>
<tr>
<td>Title Page</td>
<td>25</td>
<td>-.75 (.58)</td>
<td>-.41 (1.10)</td>
<td>-.83 (.30)</td>
</tr>
<tr>
<td><strong>Hypertension Clinical Trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent form</td>
<td>18</td>
<td>.95 (.41)</td>
<td>.62 (.28)</td>
<td>.97 (.57)</td>
</tr>
<tr>
<td>Title Page</td>
<td>21</td>
<td>-.81 (.51)</td>
<td>-.53 (1.1)</td>
<td>-.83 (.19)</td>
</tr>
<tr>
<td><strong>Nutrition Clinical Trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent form</td>
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<td>.80 (.67)</td>
<td>.46 (.61)</td>
<td>.84 (.69)</td>
</tr>
<tr>
<td>Title Page</td>
<td>20</td>
<td>-.84 (.40)</td>
<td>-.48 (1.1)</td>
<td>-.88 (.00)</td>
</tr>
<tr>
<td><strong>All Conditions Clinical Trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent form</td>
<td>106</td>
<td>.89 (.55)</td>
<td>.57 (.55)</td>
<td>.94 (.57)</td>
</tr>
<tr>
<td>Title Page</td>
<td>117</td>
<td>-.82 (.49)</td>
<td>-.52 (1.0)</td>
<td>-.85 (.20)</td>
</tr>
</tbody>
</table>

6.3.2 Reliability

Across all clinical trial conditions in the consent form group, internal consistency of test items was moderate to high, with alpha (α) ranging from .79 to .84. Internal consistency across all clinical trial conditions in the title page group was low to moderate, (α = .53-.68). Greater variability would be expected given that the title page group did not receive any information about the clinical trial. When information conditions were combined, alpha was very high across all clinical trial conditions (α = .89-.93) (see Table 6.4).
Table 6.4 Internal Consistency of MICCA by Clinical Trial and Information Conditions

<table>
<thead>
<tr>
<th>Clinical trial Conditions</th>
<th>Information Conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consent Form</td>
<td>Title Page</td>
</tr>
<tr>
<td>Cancer</td>
<td>.84</td>
<td>.64</td>
</tr>
<tr>
<td>Diabetes</td>
<td>.84</td>
<td>.61</td>
</tr>
<tr>
<td>Exercise</td>
<td>.80</td>
<td>.68</td>
</tr>
<tr>
<td>Hypertension</td>
<td>.82</td>
<td>.66</td>
</tr>
<tr>
<td>Nutrition</td>
<td>.79</td>
<td>.53</td>
</tr>
</tbody>
</table>

Values reported based on Cronbach’s coefficient (α)

6.3.3 Generalizability
Test performance scores were compared between clinical trial and information conditions to identify any significant differences in test performance. The results of the analysis of variance indicate that there were no significant differences in performance between clinical trial and information conditions, as indicated by overall test performance scores (F(4, 213) = .15, p = .964), generic test performance scores (F(4, 213) = 1.53, p = .194), and trial specific test performance scores (F(4, 213) = .17, p = .955). Given these findings, it was not necessary to control for the clinical trial condition during the validity analyses.

6.3.4 Validity
A one-way ANOVA was conducted to test the effect of information conditions (consent form versus title page) on overall performance. Results from this analysis revealed that participants’ overall test performance scores (i.e., total score across all test items) differed across information conditions (F(1, 221) = 682.17, p = .000), with participants in the consent form conditions performing significantly better than those in the title page conditions (M diff = 1.72, SE = .07, p = .000).

A 2x2 mixed design analysis of variance was used to examine the effect of question type (i.e., generic versus specific) and information condition on test performance. The results of this analysis yielded a significant interaction effect between question type and
information condition, \((F(1, 221) = 25.20, p=.000)\), with analysis of simple main effects indicating the consent form group performed significantly better on both generic \(M \text{ diff} = 1.29, \text{ SE} = .10, p=.000\) and trial specific \(M \text{ diff} = 1.80, \text{ SE} =.06, p=.000\) test items. Within information conditions, participants in the title page conditions performed significantly better on generic test items compared to trial specific test items \(M \text{ diff} = 24, \text{ SE} = .07, p=.001\), whereas participants in the consent form conditions performed significantly better on trial specific test items compared to generic test items \(M \text{ diff} = .27, \text{ SE} = .07, p=.000\).

### 6.3.5 Secondary Analysis

Consistent with our hypothesis, there was a significant interaction between question type, information conditions and education \((F (1, 219) = 6.79, p=.010)\). As hypothesized, participants in the title page conditions with at least a university education performed significantly better on generic test items than those with less than a university education \(M \text{ diff} = .66, \text{ SE} = .13, p=.000\). Education did not impact performance on trial specific items for those in the title page conditions \(M \text{ diff} = .03, \text{ SE}= .08, p=.672\).

Participants in the consent form conditions with higher education performed significantly better on trial specific test items than participants with less than a university education \(M \text{ diff} = .27, \text{ SE} = .08, p=.001\). Education, however, did not significantly impact performance on generic test scores \(M \text{ diff} = .15, \text{ SE} = .14, p=.280\). Significant relationships were not detected between other explored socio-demographic variables which included: age, gender and country of residence. These results could be due to the size and/or demographic distribution of the study sample.

Test performance scores (i.e., overall, generic and trial specific) were correlated for each information condition to identify whether a relationship existed between: i) trial specific and generic test items; ii) generic test items and overall test performance; and iii) trial specific test items and overall test performance. The Pearson product-moment correlation coefficients are provided in Table 6.5. All correlations were statistically significant \((p = .000)\) with the exception of the mean correlation between generic and trial specific test performance scores for the title page condition \((r =.15, p=.103)\).
Lastly, the amount of time required for participants to complete the MICCA was calculated to assess respondent burden. On average participants took 9.2 minutes to complete the MICCA with completion times ranging between 7.4 minutes to 12.0 minutes.

<table>
<thead>
<tr>
<th>Information Condition</th>
<th>Overall - Generic</th>
<th>Overall - Trial Specific</th>
<th>Generic - Trial Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent Form (N=106)</td>
<td>.82*</td>
<td>.92*</td>
<td>.54*</td>
</tr>
<tr>
<td>Title Page (N=117)</td>
<td>.95*</td>
<td>.45*</td>
<td>.15</td>
</tr>
</tbody>
</table>

Correlations based on Pearson product-moment correlation coefficient (r)
*Coefficient significant (p=.000)

**6.4 Discussion**

Results of this psychometric study provide preliminary evidence that the MICCA can be utilized in various clinical trial types and can produce reliable and valid test scores. Moreover, the MICCA takes less than 10 minutes for participants to complete, demonstrating a low respondent burden. As such, the MICCA is a practical instrument that may be suitable for use in clinical trial research.

Internal consistency of the MICCA was high (α >.70) when measured across all participant conditions and consent form conditions. This result provides evidence that the MICCA test items are homogeneous and reliable measures of informed consent comprehension. Therefore, it seems reasonable to assume that variations in participants' test performance scores may be attributed to differences in an individual's ability rather than measurement error.19 As anticipated, internal consistency was low for the title page group; since the participants within this group did not receive any relevant information about the clinical trial, greater variability between participants' performance on test items was expected.
Using the known group approach, background knowledge and understanding of consent information was evaluated through the use of generic and trial specific test items. We determined that the groups known to differ in regard to performance on the test items would be between those exposed to informed consent information (consent condition) and those not exposed (title page conditions). The known group analysis indicated that the MICCA has the capacity to distinguish between information conditions.

As hypothesized, participants in the consent form conditions performed significantly better across all test performance scores than participants in the title page conditions (p=.000). Specifically, participants in the consent form conditions consistently outperformed participants in the title page conditions on trial specific test items. Therefore, exposure to clinical trial information appears to be related to the ability to correctly answer the trial specific test items, thereby indicating that the trial specific test items appropriately measure the consent information specific to a particular trial.

In the title page conditions, Pearson’s product-moment correlation coefficient indicated that there was no significant relationship between generic and trial specific test scores (r=.152). Further analysis found that generic test performance scores were significantly better than trial specific test performance scores (p=.000). In other words, even though participants were not exposed to clinical trial information they were still able to answer generic test items. This result suggests that generic test items appropriately measure current (i.e., background) knowledge about clinical trial research but do not assess comprehension of informed consent of a specific clinical trial.

In relation to socio-demographic variables, in the title page conditions a relationship was found between education and performance on generic test items (p=.000). Participants with at least a university education performed significantly better on generic test items than those with less than a university education. Greater education may, therefore, enhance general knowledge about clinical trial research. Conversely, education significantly influenced performance on trial specific test item in the consent form conditions (p=.001). Participants with at least a university education performed significantly better on trial specific items than those with less than a university
education. These results are consistent with research that suggests there is a strong positive correlation between education and reading comprehension.\textsuperscript{27,28} Therefore, it may be that greater education attainment enhanced participants’ reading comprehension related to novel aspects about the clinical trial. However, additional research is required before drawing conclusive statements about the relationship between these variables.

To evaluate the generalizability of the MICCA, test performance of the information conditions was compared across the different clinical trial conditions. No significant differences were found. Even though these results reflect the evaluation of only five different clinical trial types, they do provide a preliminary indication that the MICCA may be applicable to various types of clinical trials.

While results of this study lend support to the reliability, validity and generalizability of the MICCA, potentially important study limitations should be recognized. The foremost limitations are in regard to representativeness of the study sample. The participants in this study consisted of a convenience sample which was highly educated. Half of the study participants had obtained at least an undergraduate degree which is not consistent with a typical clinical trial population. Descriptive studies suggest that only between 15-30\% of clinical trial participants have obtained an undergraduate degree or higher.\textsuperscript{8,14,15,29} \textbf{The distribution of education in this study’s sample may be related to the fact that having access to a computer and the internet were required to participate in this study. Redpath et al.\textsuperscript{,29} identified educational level as a significant predictor of Internet use and that most Internet users have obtained at least one college degree. Moreover, participation in clinical trial research was as much higher in this study’s sample (15.7\%) compared to the percent of the population that actually participates in clinical trials (1-5\%).}\textsuperscript{30}

Our study did not survey study participants’ experience with disease characteristics (such as disease type or number of years with a disease) or previous treatment for a given disease. These characteristics could significantly influence performance on a comprehension test such as the MICCA. Therefore it could not be determined whether such an interaction existed. Lastly the number of clinical trial informed consent documents utilized in this
study was quite limited making it difficult to generalise the results to other types of clinical trials not represented in this study.

In order to establish stronger psychometric evidence, additional assessments are recommended. We suggest that an appropriate next step would be to conduct a larger scale implementation study. For greater representation of the clinical trial process the study should include a sample of actual clinical trial participants and/or those who have expressed intent to take part in a clinical trial. Broader international representation may provide additional information about the generalizability of the instrument across cultures. As well, representation of different types of clinical trials may provide additional evidence of generalizability. Further investigation in regards to the impact of education on participants’ comprehension of clinical trial information is another potential area of future research. Perhaps individuals educated in sciences or health-related disciplines would perform better on the MICCA than participants from non-health-related disciplines (e.g., English literature or music).

This preliminary psychometric study indicates that the generic and trial specific test items that make up the MICCA measure the construct of informed consent comprehension as defined by Buccini et al. These findings are potentially significant for clinical trial researchers interested in utilizing a comprehension instrument during the participant recruitment process. Instruments containing generic test items would appear to primarily evaluate understanding of general clinical trial knowledge. Trial specific instruments may fail to assess general information related to clinical trial research, which according to this study, is less likely to be common knowledge among participants with a lower education attainment. If the objective is to measure informed consent comprehension, an instrument that integrates both generic and trial specific items, such as the MICCA, seems justified.
6.5 References


CHAPTER 7
Conclusions and Implications for Future Research

7.1 Summary
This chapter summarizes the major findings from the systematic review (Chapter 3) and the three research studies that are described in Chapters 2, 4, 5 and 6. The implications of these findings for measuring potential research participants’ comprehension of informed consent information are also discussed.

Chapter 2 describes the results of a study on the readability of a convenience sample of informed consent documents utilized in ethics approved clinical trials research. The study also examined whether readability guidelines for informed consent documents exist within Australia at the national and/or local level. Publicly available regulatory and policy documents were reviewed from the Australian National Health and Medical Research Council (NHMRC) and the two local ethics committees which had previously approved the informed consent documents under study. Although formal readability standards could not be identified, e-mail correspondence with the two local ethics committees revealed that informed consent documents are subjectively evaluated for readability by ethics committee members. The ethics committees’ subjective evaluation concluded that the informed consent documents under study were readable for HIV/AIDS and type 2 diabetes patients. However, the readability analysis found that to read the informed consent documents required, on average, at least some university education. Given that almost half of Australians have reading skills at or below an 8th grade reading level,¹ it is probable that many of the research participants would have had difficulty reading these documents. Therefore, the ethics committees’ subjective assessments used to evaluate this sample of informed consent documents may not be the most reliable or effective method for evaluating readability. Therefore, it is recommended that research ethics committees build into their research ethics application process an objective automated system for assessing informed consent readability. Unreadable informed consent documents may result in patients rejecting
trial participation altogether, or conversely, may result in their participating in a trial with inadequate consent.

The systematic review (Chapter 3) identified, critically reviewed and compared existing standardized instruments that measure clinical trials informed consent comprehension in non-cognitively impaired adults. Three instruments met the defined inclusion criteria: the Deaconess Informed Consent Comprehension Test (DICCT), the Quality of Informed Consent (QuIC) questionnaire and the Brief Informed Consent Protocol (BICEP). Adequate reliability had been established for all instruments. Psychometric evaluation of validity was only conducted for the DICCT, results indicating that the DICCT is moderately effective in measuring comprehension. An evaluation of generalizability was not conducted for any of the instruments. It appears much more psychometric analyses are needed to determine whether the instruments are appropriate for the measurement of informed consent comprehension in non-cognitively impaired adults. Moreover, there was significant variability between the instruments in terms of how the instruments were constructed and the content that they measured; this may be due to the absence of an accepted construct definition of informed consent comprehension. A construct definition operates to standardize the process of constructing an instrument and applying it into practice.

Chapter 4 was devoted to developing a construct definition of informed consent comprehension. The Delphi approach was utilized with an international expert panel (N=19) to gather knowledge, opinions and eventually consensus for a construct definition of informed consent comprehension. Expert consensus on a definition was achieved after three revisions to the definition. Significantly, this definition specifies the realm of information that should be measured by comprehension instruments (i.e. content domain), indicates how test items should be constructed, and specifies when comprehension should be assessed. While there are limitations to the study, it nonetheless should be considered as a step toward standardization of a construct definition of informed consent comprehension. Developing a standard method of communicating about informed consent comprehension could have a significant impact on how the construct of informed consent comprehension is measured and how subsequent instruments are developed.
Chapter 5 presents a comprehensive methodology for constructing two instruments, the Brief Investigator Survey (BIQ) and the Modular Informed Consent Comprehension Assessment (MICCA). The MICCA is the core instrument designed based on the construct definition proposed in Chapter 4 and functions to measure comprehension of informed consent information. The MICCA was developed using a combination of generic and trial specific test items. This approach was utilized to satisfy the criteria of the construct definition, which states that informed consent comprehension is the product of integrating current knowledge with trial-specific informed consent information. The BIQ was developed as a companion instrument that functions to create the trial specific test items within the MICCA; these items are customized to reflect the design characteristics and research protocols of a particular clinical trial. An assessment of construct validity by four clinical trialists provided preliminary evidence that the MICCA measures the construct of informed consent comprehension as defined in Chapter 4. MICCA and the BIQ hold promise as instruments that can be utilized across a range of clinical trials to assess comprehension in terms of general knowledge about clinical research as well as specific aspects about a particular clinical trial. However, to establish whether the MICCA could be utilized to inform clinical decision making, psychometric testing of the MICCA was required.

Chapter 6 describes and reports the outcomes of a preliminary study conducted to assess the reliability, generalizability, and validity of the MICCA. The results of the psychometric study indicate that MICCA test items demonstrate moderate to high internal consistency. There were no significant differences in test performance across different types of clinical trials which signifies that the MICCA may be generalizable across different clinical trials. The evaluation of known group validity suggests that the generic and trial specific test items that make up the MICCA measure the construct of informed consent comprehension as defined in Chapter 4. These results suggest that informed consent comprehension instruments containing generic test items may only evaluate understanding of general knowledge regarding clinical trial research. On the other hand, trial specific instruments may fail to assess general information related to clinical trial research, which according to this study, is less likely to be common knowledge among participants with low education attainment. If the objective is to
measure informed consent comprehension, an instrument that integrates both generic and trial specific items, such as the MICCA, may be required.

**7.2 Limitations and Suggestions for Future Research**

There are several limitations to the research studies presented in this thesis that warrant consideration and should be addressed in future studies. In particular, the sample of informed consent documents assessed in the readability study was relatively small and only based on HIV/AIDS and type 2 diabetes clinical trials. Readability studies that include a larger sample of informed consent documents from a variety of different types of clinical trials may provide greater understanding of the complexity of informed consent documents utilized in clinical trials conducted within Australia. Also noteworthy would be a study which identifies ethics committees (within Australia and from other countries such as the United States, Canada and United Kingdom) that have readability standards incorporated into their ethics review process. The effectiveness of the ethics committees’ procedures for assessing and monitoring the readability of informed consent warrants investigation. This information may be useful to other ethics committees which might be interested in implementing readability standards into their ethics review process.

The primary limitation to the construct definition study presented in Chapter 4 is the size and composition of the expert panel. It is recommended that a larger sample of individuals with more diverse geographic representation be recruited to evaluate the proposed definition and attempt to address unresolved issues related to the definition. For example, the construct definition specifies that comprehension of informed consent information includes an understanding of national and international ethics regulations. However, there is wide diversity of ethical requirements that exist across countries. Perhaps it would, therefore, be possible to establish a core set of research consent requirements that are applicable within and across different countries. Discussion is also needed regarding whether the various consent requirements, as they stand, represent what they were intended to represent or whether they in fact need to be revised. Furthermore, the proposed construct definition does not address how much comprehension is enough comprehension for consent to be considered informed.
As described in Chapter 5, the MICCA was developed to measure comprehension related to the informed consent disclosure requirements from the United States, Canada, and Australia. As a consequence, the MICCA may not be an applicable measure of comprehension in clinical trials conducted outside of these countries. However, the MICCA could be further developed to account for this limitation by including additional test items that measure consent requirements specified by other countries.

Furthermore, additional BIQ and MICCA test items could be developed that are phase specific or based on a certain disease state. In other words, questions could be programmed into the BIQ to generate MICCA test items that are specific to the phase of the clinical trial (e.g., Phase I-Phase IV) or the disease state associated with the clinical trial (e.g., HIV, oncology). However if additional test items are developed, caution should be taken in regards to the total number of test items that appear on the MICCA. Including too many test items runs the risk of over-burdening the test taker and increasing administrative burden associated with distributing the test; this could have the effect of limiting the uptake of instruments into practice.

A major limitation to the psychometric evaluation of the MICCA (Chapter 6) is related to the participant sample. Individuals evaluated for informed consent comprehension in the study may not be representative of participants who actually enrol onto clinical trials. For greater representation subsequent evaluations of the MICCA should include a sample of actual clinical trial participants or those who have expressed intent to participate in a clinical trial. As well, more extensive international representation of participants from more diverse types of clinical trials (different phases of clinical trials and clinical trials which study different diseases/conditions) may provide additional information about the generalizability of the instrument across geographic regions, cultures and clinical trial setting. As well the study population ought to include individuals with different disease conditions and treatment experiences. This might provide insight to how such characteristics affect comprehension.

Additional research that considers other variables that might influence comprehension is also warranted. For example, does the type of university education (i.e. discipline of study) or the type of resources a person utilizes to gather health-related information
influence performance on the MICCA? Additionally, prior participation in clinical trial research may impact performance on generic and/or trial specific test items. Although this information was collected during the psychometric evaluation, only a few of the study participants had ever taken part in a clinical trial and, as a result, the significance of the relationship between prior clinical trial participation and test performance could not be examined.

As stated in Chapter 5, the MICCA and the BIQ work in tandem to measure research participants’ comprehension of informed consent information. However, this thesis does not include an assessment of the BIQ. Therefore, another significant area for research would be to evaluate the utility of the BIQ. Utility refers to ease and efficiency of the use of an instrument, and the relevance and meaningfulness of the information that it provides. An evaluation of utility could be conducted to assess: i) how easy it is for research investigators to respond to BIQ questions; ii) how long it takes to complete the BIQ and to generate a customized version of the MICCA, and whether the time required is acceptable to the research investigator; iii) whether BIQ questions are relevant to the research investigator’s clinical trial; iv) whether the BIQ consistently produces test items that are representative of the investigator’s clinical trial; and iv) the likelihood that an investigator would utilize the BIQ and the MICCA (generated by the BIQ) in clinical practice.

7.3 Conclusion

While a number of ethical safeguards exist to protect research participants from harm, one component of human research that requires additional safeguards is the process of obtaining informed consent. Research suggests that few participants, when enrolling onto a trial, fully understand what it is they are consenting to. Informed consent comprehension tests have therefore been developed as a method of obtaining evidence that participants’ consent to take part in a research study is truly informed. However, the available instruments are not without limitations. The psychometric properties of these instruments have not been well established and each has been developed in the absence of a construct definition, making it difficult to evaluate the instruments’ validity.
This thesis has addressed the major conceptual and methodological limitations of previously developed instruments that purport to measure informed consent comprehension. To my knowledge, the MICCA is the first informed consent comprehension instrument to be developed based on an explicitly stated construct definition. Results of the psychometric analysis provide preliminary evidence that the MICCA can be utilized in various clinical trial settings and can produce reliable and valid test scores. These findings are potentially significant for clinical trial researchers or ethics committees interested in implementing a comprehension instrument during participant recruitment.

It is intended that the MICCA will be used as a tool to enhance understanding of clinical trial information during the patient recruitment process. Incorrect responses on the MICCA should be corrected by research investigators, and thereby used as an opportunity to further educate potential participants about the clinical trial. This process can help to enhance participants’ understanding and hence, promote autonomous informed decision making regarding trial participation. With the growing legal and ethical concerns about informed consent, research investigators and research ethics committees alike should be considering methods for evaluating research participants’ comprehension of informed consent information. Evidence of comprehension through the use of comprehension tests, such as the MICCA, can help ensure that consent to participate in a research study is, in fact, informed.
7.4 References


### Appendix A - Content Domain

<table>
<thead>
<tr>
<th>Informed Consent Disclosure Requirements</th>
<th>Taken from</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A statement explaining that the trial involves research</td>
<td>CA, US (NIH &amp; FDA), GCP</td>
</tr>
<tr>
<td>2. A statement explaining the purpose of the trial</td>
<td>CA, US (NIH &amp; FDA), GCP, Lit Review</td>
</tr>
<tr>
<td>3. Explanation of randomization &amp; the probability for random assignment to each treatment</td>
<td>CA, GCP, Lit Review</td>
</tr>
<tr>
<td>group (if applicable)</td>
<td></td>
</tr>
<tr>
<td>4. Explanation of placebo (if applicable)</td>
<td>Lit Review</td>
</tr>
<tr>
<td>5. Explanation about blinding/double blinding (if applicable)</td>
<td>Lit Review</td>
</tr>
<tr>
<td>6. Explanation of trial procedures (including invasive procedures)</td>
<td>CA, US (NIH &amp; FDA), AU, GCP</td>
</tr>
<tr>
<td>7. Explanation about participants’ responsibilities</td>
<td>CA, GCP</td>
</tr>
<tr>
<td>8. Explanation about aspects of the study that are experimental</td>
<td>CA, US (NIH), GCP, Lit Review</td>
</tr>
<tr>
<td>9. Description of risks or inconveniences (including risks to unborn fetus)</td>
<td>CA, US (NIH &amp; FDA), GCP, Lit Review</td>
</tr>
<tr>
<td>10. Description of expected benefits</td>
<td>CA, US, AU, GCP, Lit Review</td>
</tr>
<tr>
<td>11. Explanation about alternative procedures/treatment (including risk and benefits of alternatives)</td>
<td>CA, US (NIH &amp; FDA), AU, GCP</td>
</tr>
<tr>
<td>12. Explanation about compensation in event of trial related injury.</td>
<td>CA, US (NIH &amp; FDA), AU, GCP</td>
</tr>
<tr>
<td>13. Explanation about any payment (monetary &amp; non-monetary) available for participating in study</td>
<td>CA, US (NIH), AU, GCP</td>
</tr>
<tr>
<td>14. Explanation about any costs participants may accrue for taking part in the study</td>
<td>CA, US (NIH &amp; FDA), GCP</td>
</tr>
<tr>
<td>15. Statement that participation is voluntary</td>
<td>CA, US (NIH &amp; FDA), AU, GCP</td>
</tr>
<tr>
<td>16. Statement that participants can withdraw from the trial at any time</td>
<td>CA, US (NIH &amp; FDA), AU, GCP</td>
</tr>
<tr>
<td>17. Description as to how patients’ data will be kept confidential and who will have access to</td>
<td>CA, US (NIH &amp; FDA), AU GCP</td>
</tr>
<tr>
<td>participants medical records</td>
<td></td>
</tr>
<tr>
<td>18. Statement about how patients will be informed of new study findings (relevant to willingness to</td>
<td>CA, US (NIH &amp; FDA), GCP</td>
</tr>
<tr>
<td>continue in the study)</td>
<td></td>
</tr>
<tr>
<td>19. Contacts for information regarding participation</td>
<td>CA, US (NIH &amp; FDA), AU, GCP</td>
</tr>
<tr>
<td>20. Explanation of situations when participant may be terminated from trial</td>
<td>CA, US (NIH &amp; FDA), GCP</td>
</tr>
<tr>
<td>21. Statement about the duration of participation</td>
<td>CA, US (FDA), GCP</td>
</tr>
<tr>
<td>22. Number of participants taking part in the study</td>
<td>US (NIH &amp; FDA), GCP</td>
</tr>
<tr>
<td>23. Statement about source of funding for the research (conflicts of interest)</td>
<td>CA, US (NIH), AU</td>
</tr>
<tr>
<td>24. Understand the meaning of signing a consent form *</td>
<td>Expert feedback</td>
</tr>
</tbody>
</table>

*Added to content domain list per expert panel suggestion; AU= Australia informed consent disclosure requirements; CA= Canada informed consent disclosure requirements; US FDA= Food and Drug Administration informed consent disclosure requirements; US NIH= National Institutes of Health informed consent disclosure requirements; GCP= International Standards for Good Clinical Practice informed consent disclosure requirements; Lit Review= commonly help misconceptions as cited in the literature.
Appendix B: Modular Informed Consent Comprehension Assessment (MICCA): Full Version

1. True/False Questions

**Instructions:** Please click on the circle that best answers each statement listed below. You may ONLY CLICK ON ONE circle for each statement.

1. The clinical trial is a form of research.
   - True
   - False
   - I don't know

2. I am required to take part in the clinical trial.
   - True
   - False
   - I don't know

3. I have been told who is funding the clinical trial.
   - True
   - False
   - I don't know

4. I have been told the total number of people who will take part in the clinical trial.
   - True
   - False
   - I don't know

5. During the clinical trial I will know which treatment I am receiving.
   - True
   - False
   - I don't know

6. During the clinical trial the study doctors will know which treatment I am receiving.
   - True
   - False
   - I don't know

7. During the clinical trial no one will be allowed to see my health information.
   - True
   - False
   - I don't know

8. I will be told about new findings from the clinical trial so I can decide whether to continue to take part.
   - True
   - False
   - I don't know
9. I have been told who will pay for my treatment if I become ill or injured as a result of the clinical trial.  
   - True
   - False
   - I don't know

10. I have been given the name and phone number of the person to contact if I have questions or concerns about the clinical trial.  
   - True
   - False
   - I don't know

11. My participation in the clinical trial can be stopped without my consent.  
   - True
   - False
   - I don't know

12. I will be asked to pay for costs related to taking part in the clinical trial.  
   - True
   - False
   - I don't know

13. I will receive payment or an incentive for taking part in the clinical trial.  
   - True
   - False
   - I don't know

14. I may receive a treatment that does NOT have any therapeutic benefit (i.e. does not treat your condition).  
   - True
   - False
   - I don't know

2. Multiple Choice

Instructions: Please click on the circle that best answers each question listed below. You may ONLY CLICK ON ONE circle for each question.

15. How will it be decided which treatment group you will be placed into?  
   - The group I am placed into will be based on my health care needs
   - The group I am placed into will be randomly assigned to me
   - I am free to decide which group I would like to be placed into
   - I don't know
16. The clinical trial includes a treatment that has not been approved for your condition. What does this mean?  
- Outside of this trial, the treatment CAN be used for people with my condition  
- Outside of this trial, the treatment CANNOT be used for people with my condition  
- The treatment is the best possible for my condition  
- I don’t know  

17. How long can you expect to be in the clinical trial?  
- 26 weeks  
- 56 weeks  
- 106 weeks  
- I don’t know  

18. At what point can you leave the clinical trial?  
- I can leave at any time  
- I can only leave once all of my data has been collected  
- I can only leave once the study is over  
- I don’t know  

19. What does it mean when you sign the clinical trial consent form?  
- I would like to take part in other similar trials  
- I do NOT want to take part in this trial  
- I am agreeing to take part in this trial  
- I don’t know  

3. Check Boxes  
Instructions: Please click on the box or boxes that best answers each question listed below. You may click on MORE THEN ONE box for each question.  

20. Which describes the main purpose(s) of the clinical trial?  
- To identify how well the treatment works  
- To identify how much of the treatment can be given without causing harm  
- To improve my own medical/health condition  
- To test the safety of the treatment  
- I don’t know
21. Which procedure(s) will you be asked to take part in?  
- Blood collection
- Glucose tolerance test
- Physical exam
- X-rays
- I don’t know

22. Which task(s) will you be asked to complete?  
- Attend scheduled office/clinic visits
- Follow a specific diet
- Follow an exercise plan
- Inform study doctors before taking prescription or non-prescription drugs (including herbal remedies)
- I don’t know

23. Which side effect(s) might occur?  
- Upset stomach (nausea)
- Flu like symptoms
- Headaches
- High blood sugar
- I don’t know

24. Which describes the main benefit(s) of taking part in the clinical trial?  
- Finding treatment(s) that may help others that have my condition
- Free medical care
- Free health/medical education
- Cure or improve my own health/medical condition
- I don’t know

25. Which describes the other treatment option(s) available to you?  
- Drug treatment (prescription or non-prescription)
- Radiation treatment
- Surgical treatment
- There are NO other treatment options available
- I don’t know

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1. Generic test items- These test items appear on each version of MICCA.
2. Trial specific test items- These test items do not appear on every version of the MICCA. They are generated based on response to BIQ.
3. Trial Specific test items- These test items appear on each version of the MICCA. The response options for each of these test items are generated based on response to BIQ.
Appendix C Brief Investigator Questionnaire (BIQ)

Brief Investigator Questionnaire (BIQ)

Instructions: Your responses to the following 10 questions will be used to generate a comprehension test that is tailored to your clinical trial. Once you have answered the 10 questions click on "Submit my responses" located at the bottom of this page.

1. Will participants in the clinical trial be blinded?
   - Yes, ALL of the participants will be blinded
   - Only SOME of the participants will be blinded
   - No, NONE of the participants will be blinded

2. Will doctors/investigators in the clinical trial be blinded?
   - Yes, study doctors/investigators will be blinded to ALL arms of the study
   - Study doctors/investigators will be blinded to ONLY SOME arms of the study
   - No, study doctors/investigators will not be blinded to any arms of the study

3. Check all the following that apply to the clinical trial.
   - Randomization
   - Placebo
   - Inclusion of any investigational/experimental treatments
   - None of the above apply to my study

4. Check the main purpose(s) of the clinical trial.
   - To identify how well a treatment/procedure works
   - To identify how much of a treatment/procedure can be given without causing harm
   - To improve the participant's own medical/health condition
   - To test the safety of a treatment
   - To determine the cause of a disease

Other

Other

Other
5. Check ALL procedures that are required for participation in the clinical trial. If there are procedures not listed below that you feel are necessary for participants to understand then please list them under "other". You may list up to three "other" procedures (one per box).

- Biopsy sample
- Blood pressure reading
- Blood sample
- Body measurements (height, weight, body fat)
- CT scan
- ECG reading
- Fitness test
- Infusion
- Injection
- MRI scan

- Nutrition education
- Physical exam
- Pregnancy test
- Ultrasound scan
- Urine collection
- X-ray

There are no procedures associated with this trial

Other
Other
Other

6. Check ALL responsibilities that are require of participants in the clinical trial. If there are responsibilities not listed below that you feel are necessary for participants to understand then please list them under "other". You may list up to three "other" responsibilities (one per box).

- Attend office/clinic visits
- Fasting (restrict food/drink intake)
- Fill out surveys
- Follow a special diet
- Follow an exercise plan
- Inform study doctors before taking any prescription or non prescription drugs (including herbal remedies)
- Inform study doctors if participant or partner becomes pregnant

- Inform study doctor of any sickness or injury
- Keep a food diary
- Keep a physical activity diary
- Use only birth control approved by study doctors

There are no tasks associate with this trial

Other
Other
Other
7. Check ALL side effects that may result due to participation in the clinical trial. If there are side effects not listed below that you feel are necessary for participants to understand then please list them under "other". You may list up to three "other" side effects (one per box).

- [ ] Allergic reaction
- [ ] Anemia (decreased iron levels)
- [ ] Anxiety (nervousness)
- [ ] Bleeding (excessive)
- [ ] Blurred vision
- [ ] Bruising
- [ ] Chest congestion
- [ ] Chest pain
- [ ] Constipation
- [ ] Cough
- [ ] Decreased sex drive
- [ ] Dehydration (water loss)
- [ ] Depression (sadness)
- [ ] Diarrhea
- [ ] Dizziness
- [ ] Drowsiness
- [ ] Fatigue (weakness)
- [ ] Gas/bloating
- [ ] Hair loss
- [ ] Headaches
- [ ] Hot flashes
- [ ] Hyperglycemia (increased blood sugar levels)
- [ ] Hypertension (increased blood pressure)
- [ ] Hypoglycemia (low blood sugar levels)
- [ ] Hypotension (low blood pressure)
- [ ] Incontinence (inability to control urine stream)
- [ ] Infection
- [ ] Insomnia (inability to sleep)
- [ ] Irritability
- [ ] Joint soreness/stiffness
- [ ] Loss of appetite
- [ ] Mood swings
- [ ] Muscle cramps/aches
- [ ] Nausea (upset stomach)
- [ ] Neutropenia (decreased white blood cell count)
- [ ] Osteoporosis (thinning of bones)
- [ ] Rash
- [ ] Seizures
- [ ] Shortness of breath
- [ ] Sore throat
- [ ] Stomach pain
- [ ] Swelling
- [ ] Thirst (increase)
- [ ] Thrombocytopenia (reduced platelet count)
- [ ] Vomiting
- [ ] Weight gain
- [ ] Weight loss
- [ ] There are no side effects related to this trial

Other

Other

Other

8. Check ALL benefits expected from participating in the clinical trial. If there are benefits not listed below that you feel are necessary for participants to understand then please list them under "other". You may list up to three "other" benefits (one per box).

- [ ] Long-term healthcare follow-up
- [ ] Payment for participation
- [ ] Assist in finding a treatment that will help others with the same condition
- [ ] Obtain free medical care
- [ ] Receive a medical or health evaluation
- [ ] Possibility of patient's own condition improving
- [ ] There are no benefits associated with this trial

Other

Other

Other
9. What are alternative treatment options available to participants outside of the clinical trial?
If there are treatment options that are not listed below that you feel are necessary for participants to understand then please list them under "other". You may list up to three "other" alternative treatment options (one per box).

- [ ] Drug treatment
- [ ] Psychological treatment
- [ ] Radiation treatment
- [ ] Surgical treatment
- [ ] Diet modification
- [ ] Physical activity
- [ ] Weight loss
- [ ] There are no alternative treatment options available

Other

Other

Other

10. How long is participation in the clinical trial expected to last?
In the box provided enter a duration of time. NUMBERS and DASH ONLY, NO SPACES (Example: "57" or "45-67")

[ ] hour(s) [ ] day(s) [ ] week(s) [ ] month(s) [ ] year(s)
Appendix D.1 De-identified Cancer Informed Consent Document

Informed Consent to Participate in a Clinical Trial Research Study

**Study Title:** A Randomised Trial Evaluating Vasta as Adjuvant Treatment for Cutaneous Melanoma

**Sponsor:** Pharma X Ltd.

**Protocol No:** D 000-000 01

**Investigator:** Professor J Smith

Clinical Trial & Research Unit: Ph 00 1111 2222

INTRODUCTION

You have just undergone surgery to remove melanoma. The standard way we follow-up with people like yourself is for a physician to see you very regularly in case your melanoma comes back (called a recurrence). It is known that you are at significant risk of recurrence. There are medications available that may help to decrease the potential for recurrence but many of these medications have unpleasant side effects, so they are not given to melanoma patients. Vasta is a new anti-cancer medication. It is currently being tested in a variety of different types of cancer, with some promising results.

WHAT IS THE PURPOSE OF THIS STUDY?

We would like to invite you to participate in a clinical trial, a type of research study, to find out whether a medication called ‘Vasta’ can prevent the recurrence of melanoma. This study will test the safety and the effects (good and bad) of patients who take Vasta compared with patients receiving standard care (regular doctor follow-up). Vasta is an investigational drug for the treatment of melanoma recurrence. This means that Vasta has not approved to treat melanoma recurrence and therefore cannot be given to patients outside of this study.
HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?
This study will initially involve a total of 300 patients.

WHO IS THE SPONSORING THE STUDY?
The study is sponsored by a pharmaceutical company called Pharma X. Your study doctor or hospital will be paid to cover the costs of you participating in this study.

HOW DO I KNOW IF I AM ABLE TO PARTICIPATE IN THIS STUDY?
Anyone who has undergone surgery in the past month to remove a melanoma may be eligible to participate in this study. Women who are pregnant, intend to become pregnant or are breast feeding will not be able to participate. For more information see the section below labeled: ‘PREGNANCY AND BREAST FEEDING’. As well those who suffer from certain medical conditions may not be able to participate in this study. These conditions will be discussed with you by the study doctor.

TREATMENT GROUPS
If you choose to participate in this study, you will be randomly allocated to 1 of 2 treatment groups. This means that you and your doctor will NOT decide which of the 2 groups you will be placed into. In other words, the group you are placed in will be determined purely by chance.

- **Group A**: If you are randomly assigned to Group A you will be observed very closely on a regular basis by the study doctor. This is currently the standard method for managing people who have had melanoma surgically removed.
- **Group B**: If you are randomly assigned to Group B you will receive Vasta. Vasta is given intravenously once every 3 weeks. It is an outpatient treatment which lasts approximately 30 minutes.

HOW LONG WILL I BE IN THE STUDY?
The study will last up to 1 year. If you are assigned to Group B (Vasta group) you will undergo a maximum of 17 treatments over the course of 1 year. Treatment may stop sooner if your tumour recurs, if you experience unpleasant side effects or your doctor feels it is in your best
interest to stop. Once treatment with Vasta stops, you will be followed up closely by a physician in the same way as patients in Group A.

**STUDY PROCEDURES**

All participants in Group A and Group B will be required to attend the clinic once every 3 weeks for a year. During these clinic visits you will undergo the following procedures:

- An intravenous treatment of Vasta **(Group B ONLY)**
- A Physical examine
- A Blood test
- A chest x-ray
- An ECG (electrocardiogram which measures electrical activity of your heart)
- A CT scan of your body and head to make sure there is no visible tumour
- A urine sample

**WHAT HAPPENS IF THE MELANOMA RETURNS?**

If there is concern that the melanoma has returned, you may have a scan and/or a biopsy, as appropriate. You may be referred back to the surgeons or alternative treatments may be discussed with you. You may be asked to stop being in the study if the study doctor has concerns about your health.

**WHAT SIDE EFFECTS OR RISKS CAN I EXPECT**

Vasta is now routinely used to treat patients with bowel cancer and is likely to become a standardised treatment for other common cancers in the near future. Most of the serious side effects described below have occurred in patients receiving chemotherapy drugs combined with Vasta. Studies suggest that Vasta taken alone is overall, well tolerated.

**Most common side effects include:**

- protein in the urine
- raised blood pressure
- diarrhea
- nausea
- fatigue
Life threatening events which have occurred include:

- heart failure
- severe bleeding
- allergy reactions

For this reason, people at risk of any of these serious complications will not be able to enter the study.

**WHAT HAPPENS IF I EXPERIENCE ANY OF THESE SIDE EFFECTS?**

You will be monitored closely throughout the study for any side effects. However, we may need to interrupt your treatment if these side effects occur. Sometimes, we may feel you need to stop treatment altogether because of the side effects. In addition, you will always be able to stop participating in this study at any time.

**PATIENT RESPONSABILITIES**

As a participant in this study you are responsible for completing the following tasks:

- Contact your study doctor if you experience any side effects which interrupt your daily life --whether you think the treatment has caused them or not.
- Tell your study doctor if you start any new medication. This includes prescription, non-prescription, herbal or alternative medicines.
- It is very important that you do not take aspirin without informing your study doctor.
- Tell your doctor if you or your partner becomes pregnant any time during this study.
- Complete a ‘Quality of Life’ questionnaire

**WHAT IF I AM PREGNANT OR BREAST FEEDING**

The effect of the study medication, Vasta, on the unborn child is unknown and therefore women should not participate in this study if they are pregnant, breast-feeding or intend to become pregnant during the study. Women still having periods will need to have a pregnancy test (blood or urine) before taking part. Women randomised into Treatment Group B (Vasta group) must agree to use non-hormonal contraceptives. Women should continue to use this type of contraception for at least 6 months after treatment has completed.
Examples of approved birth control include:

- Condom
- Intra-uterine device (IUD) plus condom
- Diaphragm with spermicide plus condom

If you are receiving Vasta and you, or your partner, become pregnant during the treatment period you must tell your study doctor immediately so appropriate action can be discussed.

WHAT ARE THE BENEFITS OF TAKING PART IN THIS STUDY?
We hope to find out whether the new medication, Vasta, is a useful treatment to prevent melanoma recurrence. There is no guarantee of direct benefit to you, but the information from this study could help manage recurrence of melanoma in future patients.

WILL I BE TOLD ABOUT THE RESULTS OF THIS STUDY?
YES. You will be told by the study doctor or staff if new information becomes available that might influence your decision to continue to participate in the study.

WILL MY MEDICAL INFORMATION BE KEPT CONFIDENTIAL?
YES. All data about you will be kept confidential. The study doctor and staff will not use your name when they enter your data. Data from this study that is published or presented at scientific conferences will not include your name or any other personal information. You also have the right to look at your data and can ask for data to be reviewed according to local law.

Organizations that may look at and/or copy your medical records or review your data for research, quality assurance, and data analysis purposes include:

- Authorize staff at Pharma X
- Members of health authorities
- Ethics committees
- Other persons required by law may review the data
- If you agree, your doctor will be informed that you will be taking part in this study.
DO I HAVE TO PARTICIPATE IN THIS STUDY?

NO. It is your choice whether or not you want to participate in this study. If you decide not to participate in this study this will NOT in any way alter your medical care. If you agree to participate, you may withdraw from the study at any time without giving a reason. Your GP (family physician) will be kept informed of your progress if you consent to him/her being informed of your participation in this study.

As well, the study doctor or Pharma X may ask you to stop taking part in this study at any time if he/she believes it is best for you and your health.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT PARTICIPATE IN THIS STUDY?

Other medications are available to you if you do not want to participate in this study. Some alternative medications may have unpleasant side effects. As well, you may wish to undergo standard care for your condition, which simply includes close physician monitoring for the recurrence of the melanoma. Your doctor can discuss with you which treatment options may be best for you.

WILL I BE PAID FOR TAKING PART IN THIS STUDY?

NO. You will not receive any direct payment for participating in this study.

ARE THERE COSTS ASSOCIATED WITH TAKING PART IN THIS STUDY?

NO. There will be no charge to you for taking part in this study including office visits, medical exams and medication. As well you may be reimbursed for the cost of travel to your clinic visits if they become too costly. You should discuss any travel issues with the study doctor or staff.
WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY
You should tell the study doctor right away if you feel you have been injured due to your participation in this study. The sponsor of the study will pay for the treatment of injury that is a direct result of the study drug or study tests. A copy of this can be given to you upon request. You DO NOT give up any legal rights for injury payment by signing this consent form.

WHO CAN ANSWER MY QUESTION ABOUT THE STUDY?
You can talk to Dr. Smith about any question or concerns you have about this study at 00 1111 2222.

This study has been reviewed by the Human Research Ethics Committee (HREC). If you have any concerns or complaints about the way in which the research is or has been conducted or questions about your rights then please contact the Complaints officer HREC, on 22 4444 5555.

If you seek emergency care, or if hospitalization is required, please let the treating doctor know that you are enrolled in a research study being conducted by Dr. Smith.
CONSENT FORM

I ______________________ (insert name)_____________________ have been given the details about the research study. I have been given information about the known side effects and possible risks of the study drug. I have also been told about study procedures that I may receive.

I am free to accept or refuse to participate in this research study. I can stop taking part in the study at any time without giving a reason. If I do decide to stop taking part in the study, it will NOT have an affect on my treatment. I will not lose my rights to treatment. I will also be offered other types of treatment if I choose to stop taking part of the study.

I agree that the data collected for this study will be used as stated. I realize Pharma X may need to review the research data. My data will not have my name on it or any other information that would link the data back to me.

I agree that access to my health records may be given to authorized people at Pharma X and national/international authorities. My health records and / or study notes may need to be reviewed by study staff at sites other than the sites that I attend. I agree to this process.

I will not lose any rights that I have under local law by signing this form.

I have read and understand the information given to me in this informed consent form. I have been given the option to ask questions. All of my questions have been answered. I may contact Dr. J Smith if I have any more questions about taking part in this study.

I will be given a signed and dated copy of this Informed Consent Document.

______________________________  __________________________  __________________________
Print Name of Patient              Date                        Signature

______________________________  __________________________  __________________________
Print Name of Researcher           Date                        Signature
Informed Consent to Participate in a
Clinical Research Study

PARTICIPANT INFORMATION SHEET

PROTOCOL TITLE
A Randomised Trial Evaluating Vasta as Adjuvant Treatment for Cutaneous Melanoma
Appendix D.3 Cancer MICCA

1. True/False Questions

Instructions: Please click on the circle that best answers each statement listed below. You may ONLY CLICK ON ONE circle for each question.

1. The clinical trial is a form of research.
   - True
   - False
   - I don't know

2. I am required to take part in the clinical trial.
   - True
   - False
   - I don't know

3. I have been told who is funding the clinical trial.
   - True
   - False
   - I don't know

4. I have been told the total number of people that will take part in the clinical trial.
   - True
   - False
   - I don't know

5. During the clinical trial no one will be allowed to see my health information.
   - True
   - False
   - I don't know

6. I will be told about new findings from the clinical trial so I can decide whether to continue to take part.
   - True
   - False
   - I don't know
Appendix D.3 Cancer MICCA

7. I have been told who will pay for my treatment if I become ill or injured as a result of the clinical trial.
   
   True
   False
   I don't know

8. I have been given the name and phone number of the person to contact if I have questions or concerns about the clinical trial.
   
   True
   False
   I don't know

9. My participation in the clinical trial can be stopped without my consent.
   
   True
   False
   I don't know

10. I will be asked to pay for costs related to taking part in the clinical trial.
    
    True
    False
    I don't know

11. I will be paid for taking part in the clinical trial.
    
    True
    False
    I don't know
Appendix D.3 Cancer MICCA

2. Multiple Choice

Instructions: Please click on the circle that best answers each question listed below. You may ONLY CLICK ON ONE circle for each question.

12. How will it be decided which group you will be placed into?
   - The group I am placed into will be based on my health care needs
   - The group I am placed into will be randomly assigned to me
   - I am free to decide which group I would like to be placed into
   - I don't know

13. The clinical trial includes a treatment that has not been approved for your condition. What does this mean?
   - Outside of this trial, the treatment CAN be used for people with my condition
   - Outside of this trial, the treatment CANNOT be used for people with my condition
   - The treatment is the best possible for my condition
   - I don't know

14. How long can you expect to be in the clinical trial?
   - 1 year
   - 3 years
   - 7 years
   - I don't know

15. At what point can you leave the clinical trial?
   - I can leave at any time
   - I can only leave once the study is over
   - I can only leave once all of my data has been collected
   - I don't know

16. What does it mean when you sign the clinical trial consent form?
   - I would like to take part in other similar trials
   - I do NOT want to take part in this trial
   - I am agreeing to take part in this trial
   - I don't know
Appendix D.3 Cancer MICCA

3. Check Boxes

Instructions: Please click on the box or boxes that best answers each question listed below. You may click on MORE THEN ONE box for each question.

17. Which describes the main purpose(s) of the clinical trial?
   - To identify how well the treatment works
   - To identify how much of the treatment can be given without causing harm
   - To improve my own medical/health condition
   - To test the safety of the treatment
   - I don't know

18. Which procedure(s) will you be asked to take part in?
   - Blood collection
   - Physical exam
   - X-ray
   - ECG scan
   - I don't know

19. Which task(s) will you be asked to complete?
   - Follow a special diet
   - Inform study doctors/investigators if you or your partner becomes pregnant during the study
   - Inform study doctors before taking prescription or non-prescription drugs (including herbal remedies)
   - Inform study doctors/investigators if you become sick or injured during the study
   - I don't know

20. Which side effect(s) might occur?
   - Diarrhea
   - Heart failure
   - Proteinuria (protein loss through urine)
   - Nausea
   - I don't know
21. Which describes the main benefit(s) of taking part in the clinical trial?

- Finding treatment(s) that may help others that have my condition
- Free medical care
- Free health/medical education
- Cure or improve my own health/medical condition
- I don't know

22. Which describes the other treatment option(s) available to you?

- Drug treatment (prescription or non-prescription)
- Radiation treatment
- Surgical treatment
- There are NO other treatment options available
- I don't know
Appendix D.3 Cancer MICCA

4. About You

Instructions: Please tell us about yourself by clicking on the circle that best answers each question listed below. You may ONLY CLICK ON ONE circle for each question.

23. How old are you?
   - Younger than 40
   - 40-49
   - 50-59
   - 60-69
   - 70+

24. Where do you live?
   - Australia
   - Canada
   - New Zealand
   - United Kingdom
   - United States
   - Other

25. What is your gender?
   - Male
   - Female

26. Which best describes your background?
   - Aboriginal/Torres Strait Islander
   - African American
   - Asian
   - Caucasian
   - Latino
   - Maori
   - Pacific Islander
   - Other
27. Which describes the highest level of education you have completed?

- Primary school
- Secondary school
- Technical/vocational education
- Some university education
- Completed an undergraduate degree
- Completed a higher graduate degree (Masters, PhD etc.)

28. Have you ever taken part in a clinical trial?

- Yes
- No
- I don't know

29. Please tell us (by clicking in the circles below) how often you use the following resources to gather health information. Please click on ONLY one circle for each item.

<table>
<thead>
<tr>
<th>Resource</th>
<th>Always</th>
<th>Sometimes</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Books/Journals</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Friends/Family</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Health care provider (Drs, nurses etc)</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Internet</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Popular magazines</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Radio</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>TV/Movies</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

You have now completed the survey. Thank you for taking the time to assist us with this study.
INTRODUCTION

You have been asked to participate in a clinical trial, a type of research study, for a new medication that treats type 2 diabetes. Clinical trials only include people who choose to participate. Before you agree to participate in this research study, it is important that you read and understand the following explanation of the study and the scheduled procedures. You may want to discuss your decision with family, friends or your doctor.

WHAT IS THE PURPOSE OF THIS STUDY?

Renaglipitin may help to control blood sugar in those with type 2 diabetes. This clinical research study will test the safety and the effects (good and bad) of Renaglipitin for the treatment of type 2 diabetes when added to diet and exercise management. The results of Renaglipitin treatment will be compared to participants that received a placebo (a tablet that does not contain any active ingredients). Renaglipitin is an investigational drug). In other words, outside of this research study Renaglipitin has not been approved to treat type 2 diabetes.

You are being asked to take part in this study because your type 2 diabetes is currently not under control. Renaglipitin will be tested in participants with type 2 diabetes who have blood
sugars above normal, who have never taken medication for their diabetes or have only taken medication for their diabetes for a very short time.

**HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**
Approximately 510 participants will be enrolled onto this study in approximately 150 research centers worldwide.

**WHO IS THE SPONSORING THE STUDY?**
The study is sponsored by Pharma X. Your study doctor or hospital will be paid to cover the costs of you taking part in this study.

**HOW DO I KNOW IF I AM ABLE TO TAKE PART IN THIS STUDY?**
**The Screening Period:** During the screening period we will find out if you meet the basic requirements needed to take part in this study. There are 2 phases of the screening period.

**Phase 1:**
- The study doctor will explain the study to you
- You will be able to ask questions and decide if you want to take part in the study
- If you would like to take part in the study, you will need to sign and date this consent form

**STEP 2**
If you agree to take part in this study you will then be asked to complete the following:
- Give blood samples
- Give 1-2 urine samples
- Take a physical exam
- Take a pregnancy test if you are able to have children
- Review your medical history with the study doctor
From the results of these assessments the study doctor will be able to tell if you qualify to participate in this study.

**TREATMENT GROUPS**
If the results of the screening find that you qualify to participate in this study then you will be Randomised into 1 of 2 study groups. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your
doctor can choose the group you will be in. If you do not qualify for this study you will receive standard care to treat your type 2 diabetes. The study doctor will discuss the standard treatment methods with you.

**Group A (Renagliptin 2.5 mg):**
If you are randomised into Group A you will be:
- Given details about diet, exercise and how to use blood sugar meters (meters given to you)
- Given a kit that includes Renagliptin 2.5 mg. You will be asked to take 1 tablet every morning before your morning meal.

**Group B: Placebo**
If you are randomised into Group A you will be:
- Given details about diet, exercise and how to use blood sugar meters (meters given to you)
- Given a kit that includes Placebo medicine (like sugar pills). You will be asked to take 1 tablet every morning before your morning meal.

This is a Double Blind Study. This means that both you and your doctor will NOT know which treatment group (Group A or Group B) you have been placed into. But, if this information is needed, it is available.

**STUDY PROCEDURES**
As part of this study you will be required to attend 1 office visit per month.

**During office visits you will be asked to:**
- Take a physical exam
- Take Blood pressure and heart rate tests
- Give Blood
- Take a Pregnancy test for those able to have children
- Take an Oral Glucose Tolerance Test (takes up to 4 hours to complete)
During the office visit your doctor will:
- Review medications that you have taken since last visit
- Review changes in your health and any side effects that you have experienced
- Review your diet and exercise program

PATIENT RESPONSABILITIES
As a participant in this study you are responsible for completing the following tasks:
- Follow a diet and exercise program designed for people with diabetes
- Attend office visits during the study
- Take your own blood sugar readings at home with the meter given to you
You must inform the study doctor if you:
- Have a history of kidney disease
- Are also taking medicine for congestive heart failure
- If you or your partner becomes pregnant at any time during this study

HOW LONG WILL I BE IN THE STUDY?
Your may be in the study for up to 106 weeks.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT
You may experience some side effects related to participating in this study. Doctors do not know all the side effects that may occur. Side effects may be mild or very serious. For your safety, the study doctor will review your past medical history and closely watch you and your health during the study. You may be asked to stop being in the study if the study doctor has concerns about your health. If you are asked to stop the study, the study doctor will continue to watch you until the condition or test results go back to normal.

Side Effects of Renagliptin
In other studies about 545 people with type 2 diabetes received Renagliptin at similar and higher doses. The side effects from these studies are listed in Table-1.
### Table- 1: Side Effects of Renagliptin

<table>
<thead>
<tr>
<th>Most common</th>
<th>Less Common</th>
<th>Rare but severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head aches</td>
<td>• Joint soreness / stiffness</td>
<td>Flue like symptoms</td>
</tr>
<tr>
<td></td>
<td>• Urinary tract infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sore throat and stuffed up nose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cough</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Upset stomach (nausea)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High in blood sugar (hyperglycemia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Low blood sugar (hypoglycemia)</td>
<td></td>
</tr>
</tbody>
</table>

### Side Effects of Drawing Blood

At each office visit and during the study screening we will need to draw blood from you. Drawing blood may result in: fainting, swollen or sore veins, pain or bruising, bleeding at the site of the needle, and/or small risk of infection.

### WHAT IF MY BLOOD SUGAR BECOMES TOO HIGH OR TOO LOW?

#### High Blood Sugar (hyperglycemia):

During the study your blood sugar may get too high. If you are put into the placebo group (Group B) this may be more likely to happen. If your blood sugar remains high you may need to stop taking part in the study.

#### Low Blood Sugar (hypoglycemia):

During the study your blood sugar may get too low. You should record your blood sugar level and the things that took place before your blood sugar dropped. A logbook will be given to you at the start of the study. If your low blood sugar is not kept under control it could result in a coma, seizures, or even death. For health reasons you may need to stop taking part in the study if your blood sugar remains low.
ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
By participating in this study you will receive free education about diet and exercise that is tailored to your health care needs. You will also receive all or your medical care including medication for free. As well, doctors hope that Renaglptin will improve blood sugar control in people with type 2 diabetes but there is not proof of this yet. We do know that the results from this study will help doctors learn more about Renaglptin as a treatment for type 2 diabetes. This information could help future type 2 diabetes patients.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?
You do not have to be in this study to get treatment for your type 2 diabetes. There are other approved medications available. Your doctor can discuss with you which treatment options may be best for you.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?
YES. All data about you will be kept private. The study doctor and staff will not use your name when they enter your data. Data from this study that is published or presented at scientific meetings will not include your name or any other personal information. You also have the right to look at your data and can ask for data to be reviewed according to local law.

Organizations that may look at and/or copy your medical records or review your data for research, quality assurance, and data analysis include:

- Authorize staff at Pharma X
- Members of health authorities
- Ethics committees
- Other persons required by law may review the data
- If you agree, your doctor will be informed that you will be taking part in this study.

WILL I BE TOLD ABOUT THE RESULTS OF THIS STUDY?
YES. You will be told by your doctor or his staff if new information becomes available that might affect your decision to continue to participate in the study.
WILL I BE PAID FOR TAKING PART IN THIS STUDY?
NO. You will not receive any direct payment for taking part in this study.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?
There will be no charge to you for taking part in this study including office visits, medical exams and medication. As well you may be reimbursed for the cost of travel for your office visits if they become too costly. You should discuss any travel issues with the study doctor or staff.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY
You should tell the study doctor right away if you feel you have been injured because of taking part in this study. The sponsor of the study will pay for the treatment of injury that is a direct result of the study drug, study tests or other study procedures. You DO NOT give up any legal rights for injury payment by signing this consent form.

CAN I STOP BEING IN THE STUDY?
Yes. Your participation in this study is voluntary. You can decide to stop at any time. If you do decide to stop taking part in the study, you will be asked to go to a final office visit. During this visit your study doctor will tell you how to stop taking the drug safely and discuss other treatment options with you.

As well, the study doctor or Pharma X may ask you to stop taking part in this study at any time if he/she believes it is best for you and your health. The study may be stopped due to:

- An event or health condition that places your health at risk
- Not taking the study tablets
- Not taking blood glucose readings
- Not keeping your doctors appointments
- Any other reasons.
WHO CAN ANSWER MY QUESTION ABOUT THE STUDY?

You can talk Dr. Smith about any question or concerns you have about this study at 00 1111 2222.

This study has been reviewed by the Human Research Ethics Committee (HREC). If you have any concerns or complaints about the way in which the research is or has been conducted or questions about your rights then please contact the Complaints officer HREC, on 11 4444 5555.

If you seek emergency care, or if hospitalization is required, please let the treating doctor know that you are enrolled in a research study being conducted by Dr. Smith.
I ____________________________ have been given the details about the research study. I have been given information about the known side effects and possible risks of the study drug. I have also been told about study procedures that I may receive.

I am free to accept or refuse to take part in this research study. I can stop taking part in the study at any time without giving a reason. If I do decide to stop taking part in the study it will **NOT** have an affect on my diabetes treatment. I will not lose my rights to treatment. I will also be offered other types of treatment if I choose to stop taking part of the study.

I agree that the data collected for this study will be used as stated. I realize that Pharma X may need to review the research data. My data will not have my name on it or any other information that would link the data back to me.

I agree that access to my health records may be given to authorized people at Pharma X and national/international authorities. My health records and/or study notes may need to be reviewed by study staff at sites other than the sites that I attend. I agree to this process.

I will not lose any rights that I have under local law by signing this form. I have read and understand the information given to me in this informed consent form. I have been given the option to ask questions. All of my questions have been answered. I may contact Dr. J Smith if I have any more questions about taking part in this study.

I will be given a signed and dated copy of this Informed Consent Form.

__________________________  __________________________
Print Name of Patient          Date                     Signature

__________________________  __________________________
Print Name of Researcher       Date                     Signature
Informed Consent to Participate in a
Clinical Research Study

PARTICIPANT INFORMATION SHEET

TRIAL: D 000-000 01

PROTOCOL TITLE
A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Renagliptin in Patients with Type 2 Diabetes
Appendix E.3 Diabetes MICCA

1. True/False Questions

Instructions: Please click on the circle that best answers each statement listed below. You may ONLY CLICK ON ONE circle for each statement.

1. The clinical trial is a form of research.
   - True
   - False
   - I don't know

2. I am required to take part in the clinical trial.
   - True
   - False
   - I don't know

3. I have been told who is funding the clinical trial.
   - True
   - False
   - I don't know

4. I have been told the total number of people who will take part in the clinical trial.
   - True
   - False
   - I don't know

5. During the clinical trial I will know which treatment I am receiving.
   - True
   - False
   - I don't know

6. During the clinical trial the study doctors will know which treatment I am receiving.
   - True
   - False
   - I don't know

7. During the clinical trial no one will be allowed to see my health information.
   - True
   - False
   - I don't know
Appendix E.3 Diabetes MICCA

8. I will be told about new findings from the clinical trial so I can decide whether to continue to take part.
   - True
   - False
   - I don’t know

9. I have been told who will pay for my treatment if I become ill or injured as a result of the clinical trial.
   - True
   - False
   - I don’t know

10. I have been given the name and phone number of the person to contact if I have questions or concerns about the clinical trial.
    - True
    - False
    - I don’t know

11. My participation in the clinical trial can be stopped without my consent.
    - True
    - False
    - I don’t know

12. I will be asked to pay for costs related to taking part in the clinical trial.
    - True
    - False
    - I don’t know

13. I will be paid for taking part in the clinical trial.
    - True
    - False
    - I don’t know

14. I may receive a treatment that does NOT have any therapeutic benefit (i.e. does not treat your condition).
    - True
    - False
    - I don’t know
Appendix E.3 Diabetes MICCA

2. Multiple Choice

Instructions: Please click on the circle that best answers each question listed below. You may ONLY CLICK ON ONE circle for each question.

15. How will it be decided which treatment group you will be placed into?
   - jn  The group I am placed into will be based on my health care needs
   - jn  The group I am placed into will be randomly assigned to me
   - jn  I am free to decide which group I would like to be placed into
   - jn  I don't know

16. The clinical trial includes a treatment that has not been approved for your condition. What does this mean?
   - jn  Outside of this trial, the treatment CAN be used for people with my condition
   - jn  Outside of this trial, the treatment CANNOT be used for people with my condition
   - jn  The treatment is the best possible for my condition
   - jn  I don't know

17. How long can you expect to be in the clinical trial?
   - jn  26 weeks
   - jn  56 weeks
   - jn  106 weeks
   - jn  I don't know

18. At what point can you leave the clinical trial?
   - jn  I can leave at any time
   - jn  I can only leave once all of my data has been collected
   - jn  I can only leave once the study is over
   - jn  I don't know

19. What does it mean when you sign the clinical trial consent form?
   - jn  I would like to take part in other similar trials
   - jn  I do NOT want to take part in this trial
   - jn  I am agreeing to take part in this trial
   - jn  I don't know
Appendix E.3 Diabetes MICCA

3. Check Boxes

Instructions: Please click on the box or boxes that best answers each question listed below. You may click on MORE THEN ONE box for each question.

20. Which describes the main purpose(s) of the clinical trial?
   - To identify how well the treatment works
   - To identify how much of the treatment can be given without causing harm
   - To improve my own medical/health condition
   - To test the safety of the treatment
   - I don't know

21. Which procedure(s) will you be asked to take part in?
   - Blood collection
   - Glucose tolerance test
   - Physical exam
   - X-rays
   - I don't know

22. Which task(s) will you be asked to complete?
   - Attend scheduled office/clinic visits
   - Follow a specific diet
   - Follow an exercise plan
   - Inform study doctors before taking prescription or non-prescription drugs (including herbal remedies)
   - I don't know

23. Which side effect(s) might occur?
   - Upset stomach (nausea)
   - Flu like symptoms
   - Headaches
   - High blood sugar
   - I don't know
Appendix E.3 Diabetes MICCA

24. Which describes the main benefit(s) of taking part in the clinical trial?
   - Finding treatment(s) that may help others that have my condition
   - Free medical care
   - Free health/medical education
   - Cure or improve my own health/medical condition
   - I don’t know

25. Which describes the other treatment option(s) available to you?
   - Drug treatment (prescription or non-prescription)
   - Radiation treatment
   - Surgical treatment
   - There are NO other treatment options available
   - I don’t know
Appendix E.3 Diabetes MICCA

4. About You

Instructions: Please tell us about yourself by clicking on the circle that best answers each question listed below. You may ONLY CLICK ON ONE circle for each question.

26. How old are you?
   - n Younger then 40
   - m 40-49
   - l 50-59
   - k 60-69
   - j 70+

27. Where do you live?
   - n Australia
   - m Canada
   - l New Zealand
   - k United Kingdom
   - j United States
   - k Other

28. What is your gender?
   - n Male
   - m Female

29. Which best describes your background?
   - n Aboriginal/Torres Strait Islander
   - m African American
   - n Asian
   - m Caucasian
   - n Latino
   - m Maori
   - n Pacific Islander
   - m Other
Appendix E.3 Diabetes MICCA

30. Which describes the highest level of education you have completed?

- Primary school
- Secondary school
- Technical/vocational education
- Some university education
- Completed an undergraduate degree
- Completed a higher graduate degree (Masters, PhD etc.)

31. Have you ever taken part in a clinical trial?

- Yes
- No
- I don't know

32. Please tell us (by clicking in the circles below) how often you use the following resources to gather health information. Please click on ONLY one circle for each item.

<table>
<thead>
<tr>
<th>Resource</th>
<th>Always</th>
<th>Sometimes</th>
<th>Never</th>
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<td>jn</td>
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<tr>
<td>Health care provider (Drs, nurses etc)</td>
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<tr>
<td>Internet</td>
<td>jn</td>
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<td>Popular magazines</td>
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</tr>
<tr>
<td>TV/Movies</td>
<td>jn</td>
<td>jn</td>
<td>jn</td>
</tr>
</tbody>
</table>

You have now completed the survey. Thank you for taking the time to assist us with this study.
Appendix F.1 De-identified Exercise Informed Consent Document

Informed Consent to Participate in a Clinical Trial Research Study

**Study Title:** A Blinded, Randomised Controlled Trial to Test the Benefits of Exercise on Type 2 Diabetes

**Sponsor:** Department of Health

**Protocol No.:** D 000-000 02

**Investigator:** Professor S Thompson  
Clinical Trial & Research Unit: Ph 11 2222 3333

**INTRODUCTION**

You have been asked to participate in a clinical trial, a type of research study. This study is being organised by the University of New Haven and the New Haven Hospital and funded by the Department of Health. Please read the following information carefully. Ask us if there is anything that is not clear or if you would like more information.

**WHAT IS THE PURPOSE OF THIS STUDY?**

The purpose of this study is to identify the effects that a specialised exercise program has on blood sugar (glucose) levels in people with type 2 diabetes. We will compare blood sugar levels of patients who participate in the exercise program with patients receiving standard care for their type 2 diabetes.

**WHY HAVE I BEEN ASKED TO TAKE PART IN THIS STUDY?**

You have been asked to participate in this study because you have been diagnosed with type 2 diabetes with in the past 6 months.

**HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**

Approximately 1,000 participants with type 2 diabetes will be enrolled onto this study worldwide.
WHAT WILL HAPPEN IF I DECIDE I WANT TO TAKE PART IN THE STUDY?

If you agree to participate in this study we will arrange for you to attend a screening visit. The following will take place during the Screening visit:

- We will give you more information about the study and ask you to sign an informed consent document
- We will measure your blood pressure
- We will take a blood test to assess your diabetes control
- We will ask you to take a physical fitness test (see information below about the fitness test)

After your screening session we will know if you qualify for this study. If you DO qualify you will be scheduled for your first study visit. If you DO NOT qualify for the study your type 2 diabetes will continue to be managed with the standard treatment of care.

Screening Fitness Test - Information

Wear casual clothes and shoes for walking. You will be asked to walk 1 mile as quickly as you can. If you are unable to walk 1 mile we will measure the distance that you were able to walk. We will monitor your heart rate while you are walking and the time that it takes you to walk the mile (or the distance you can manage). This information will allow us to measure how physically fit you are.

At the end of the test you will be asked to rest and we will continue to monitor your heart rate until it has returns to the rate that is was before you started walking. We will give you something to drink and you will be able to use the changing rooms and shower facilities. This physical fitness test will take approximately 1 hour.

TREATMENT GROUPS

If you qualify to join this study you will Randomly be assigned by a computer program (like flipping a coin) to one of the following treatment groups:
Group A: Standard Care
If you are placed into Group A, your treatment will be similar to the treatment you would usually receive if you were not in a clinical trial. You will also see a dietitian for advice about your diet and a doctor will take a medical history and examine you at each office visit. You will be asked to monitor your physical activity weekly by use of a pedometer and a physical activity diary.

Group B: Exercise Group
If you are placed into Group B, you will receive the same treatment as those in Group A PLUS you will be put on a specialised exercise program to help you increase your activity levels. You will be asked to monitor your physical activity weekly by use of a pedometer and a physical activity diary.

This is a Blinded Study. This means that the study doctors and study nurses will not know which treatment group you have been placed into. We will ask you not to tell the doctors or nurses the group that you have been placed into. This is to ensure that the results of the study are unbiased and as accurate as possible. If needed the doctors treating you can find out which treatment group you have been placed into.

STUDY PROCEDURES (Both Group A and Group B)
During the study you will be asked to attend the clinic on 4 different occasions:
- 1 time for the screening visit
- 1 time for the initial study visit
- 2 follow-up visit at 6 months 12 months

During your clinic visits you will be asked to complete the following procedures:
- Give blood samples
- Take a blood pressure reading
- We will measure your weight and height
- We will measure your body fat
- Complete the 1 mile fitness assessment (described above)
PATIENT RESPONSIBILITIES
As a participant in this study you are responsible for completing the following tasks:

- Follow an exercise program (Group B Only)
- Keep a diary of your physical activity
- Wear your pedometer every day
- Inform the study doctor/nurses if you begin to feel bad during your fitness test
- Informed the study doctors of any new medication that you are taking

HOW LONG WILL I BE IN THE STUDY?
You may be in the study for up to 1 year.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT
Blood tests may result in pain or bruising at the site where the blood was drawn. Those individuals allocated to the exercise group (Group B) might notice some muscle soreness due to an increase in activity levels, but this should soon pass. Overall there few risks related to this study and we do not expect that anything should go wrong. Yet, you should inform the research team if you are feeling sick or uncomfortable during this study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
YES. You will receive diabetes education from doctors and nutritionist who specialise in diabetes care. We do NOT know if this exercise program will help you control your type 2 diabetes. Yet, this study may provide information on how to help others better manage their type 2 diabetes.

DO I HAVE TO TAKE PART IN THIS STUDY?
NO. It is up to you to decide whether or not you want to participate in this study. If you do decide to participate you will be given this information sheet to keep and asked to sign an informed consent document.
CAN I STOP BEING IN THE STUDY AFTER I DECIDE TO PARTICIPATE?  
**YES.** You are free to withdraw from this study at any time. Your decision to leave the study will not affect your relationship with the university or the hospital. As well, you may be removed from this study at any time without your consent if your health is at risk, the sponsor ends the study or for any other valid reason.

ARE THERE OTHER TREATMENT OPTIONS AVAILABLE TO ME?  
**YES.** There are medications available to you to help you manage your type 2 diabetes. Dr. Thompson will discuss which treatment options are best for you.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?  
**YES.** All information collected in the course of the study will be kept strictly private. If you agree, we will inform your doctor (family physician) of your participation in the study. Results from this research will be published in medical journals and presented at scientific conferences though your name will not be linked to any of the results.

WILL I BE TOLD ABOUT THE FINDINGS OF THIS STUDY?  
**YES.** You will be told by your doctor or the study staff if new information becomes available and might influence your decision to continue to participate in the study.

WILL I BE PAID FOR TAKING PART IN THIS STUDY?  
**YES.** If you decide to participate in this study you will receive **50 Dollars** for your time.

DO I HAVE TO PAY FOR ANY STUDY RELATED COSTS?  
**NO.** There will be no charge to you for participating in this study.
WHAT HAPPENS IF I BECOME SICK OR INJURED DUE TO THIS STUDY?

You should tell the study doctor right away if you feel you have become sick or injured as a result of participating in this study. The sponsor of the study will pay for the treatment of injury that is a direct result of the study. You **DO NOT** give up any legal rights for injury payment by signing this consent form.

WHO CAN ANSWER MY QUESTION ABOUT THE STUDY?

You can talk to Dr. Thompson about any question or concerns you have about this study at 11 2222 3333.

This study has been reviewed by the Human Research Ethics Committee (HREC). If you have any concerns or complaints about the way in which the research is or has been conducted or questions about your rights then please contact the Complaints officer HREC, on 22 4444 5555.

**THANK YOU FOR TAKING THE TIME TO READ THIS CONSENT FORM**
CONSENT FORM

I __________________________ have been given the details about the research study. I have been given information about and known the side effects and possible risks of the study medication. I have also been told about study procedures that I may receive.

I am free to accept or refuse to take part in this research study. I can stop participating in the study at any time without giving a reason. If I do decide to stop participating in the study it will NOT have an affect on my treatment. I will not lose my rights to treatment. I will also be offered other types of treatment if I choose to stop participating of the study.

I agree that the data collected for this study will be used as stated. My data will not have my name on it or any other information that would link the data back to me. I agree that access to my health records may be given to only authorized people.

I will not lose any rights that I have under local law by signing this form. I have read and understand the information given to me in this informed consent form. I have been given the option to ask questions. All of my questions have been answered. I may contact Dr. S Thompson if I have any more questions about participating in this study.

I will be given a signed and dated copy of this Informed Consent Form.

_________________________ __________________________
            ____________________________
            Print Name of Patient       Date       Signature

_________________________ __________________________
            ____________________________
            Print Name of Researcher    Date       Signature
Informed Consent to Participate in a Clinical Research Study

PARTICIPANT INFORMATION SHEET

TRIAL: D 000-000 02

PROTOCOL TITLE
A Blinded, Randomised Controlled Trial to Test the Benefits of Exercise on Type 2 Diabetes
1. True/False Questions

Instructions: Please click on the circle that best answers each statement listed below. You may ONLY CLICK ON ONE circle for each statement.

1. The clinical trial is a form of research.
   - True
   - False
   - I don't know

2. I am required to take part in the clinical trial.
   - True
   - False
   - I don't know

3. I have been told who is funding the clinical trial.
   - True
   - False
   - I don't know

4. I have been told the total number of people that will take part in the clinical trial.
   - True
   - False
   - I don't know

5. During the clinical trial the study doctors will know which treatment I am receiving.
   - True
   - False
   - I don't know

6. During the clinical trial no one will be allowed to see my health information.
   - True
   - False
   - I don't know
Appendix F.3 Exercise MICCA

7. I will be told about new findings from the clinical trial so I can decide whether to continue to take part.
   - True
   - False
   - I don't know

8. I have been told who will pay for my treatment if I become ill or injured as a result of the clinical trial.
   - True
   - False
   - I don't know

9. I have been given the name and phone number of the person to contact if I have questions or concerns about the clinical trial.
   - True
   - False
   - I don't know

10. My participation in the clinical trial can be stopped without my consent.
    - True
    - False
    - I don't know

11. I will be asked to pay for any costs related to taking part in the clinical trial.
    - True
    - False
    - I don't know

12. I will be paid for taking part in the clinical trial.
    - True
    - False
    - I don't know
Appendix F.3 Exercise MICCA

2. Multiple Choice

Instructions: Please click on the circle that best answers each question listed below. You may ONLY CLICK ON ONE circle for each question.

13. How will it be decided which group you will be placed into?
   - The group I am placed into will be based on my health care needs
   - The group I am placed into will be randomly assigned to me
   - I am free to decide which group I would like to be placed into
   - I don’t know

14. How long can you expect to be in the clinical trial?
   - 1 year
   - 3 years
   - 5 years
   - I don’t know

15. At what point can you leave the clinical trial?
   - I can leave at any time
   - I can only leave once the study is over
   - I can only leave once all of my data has been collected
   - I don’t know

16. What does it mean when you sign the clinical trial consent form?
   - I would like to take part in other similar trials
   - I do NOT want to take part in this trial
   - I am agreeing to take part in this trial
   - I don’t know
3. Check Boxes

Instructions: Please click on the box or boxes that best answers each question listed below. You may click on MORE THEN ONE box for each question.

17. Which describes the main purpose(s) of the clinical trial?
   - To identify how well the treatment works
   - To identify how much of the treatment can be given without causing harm
   - To improve my own medical/health condition
   - To test the safety of the treatment
   - I don’t know

18. Which procedure(s) will you be asked to take part in?
   - Blood collection
   - Blood pressure readings
   - Body measures (height, weight etc)
   - Fitness test
   - I don’t know

19. Which task(s) will you be asked to complete?
   - Attend scheduled office/clinic visits
   - Follow an exercise plan
   - Keep a physical activity diary
   - Wear a pedometer daily
   - I don’t know

20. Which side effect(s) might occur?
   - Infection
   - Mood swings
   - Muscle soreness
   - There are no side effects related to this trial
   - I don’t know
21. Which describes the main benefit(s) of taking part in the clinical trial include:
   - Finding treatment(s) that may help others that have my condition
   - Free medical care
   - Free health/medical education
   - Cure or improve my own health/medical condition
   - I don't know

22. Which describes the other treatment option(s) available to you?
   - Drug treatment (prescription or non-prescription)
   - Radiation treatment
   - Surgical treatment
   - There are NO other treatment options available
   - I don't know
Appendix F.3 Exercise MICCA

4. About You

Instructions: Please tell us about yourself by clicking on the circle that best answers each question listed below. You may ONLY CLICK ON ONE circle for each question.

23. How old are you?
   - Younger than 40
   - 40-49
   - 50-59
   - 60-69
   - 70+

24. Where do you live?
   - Australia
   - Canada
   - New Zealand
   - United Kingdom
   - United States
   - Other

25. What is your gender?
   - Male
   - Female

26. Which best describes your background?
   - Aboriginal/Torres Strait Islander
   - African American
   - Asian
   - Caucasian
   - Latino
   - Maori
   - Pacific Islander
   - Other
27. Which describes the highest level of education you have completed?

- Primary school
- Secondary school
- Technical/vocational education
- Some university education
- Completed an undergraduate degree
- Completed a higher graduate degree (Masters, PhD etc.)

28. Have you ever taken part in a clinical trial?

- Yes
- No
- I don't know

29. Please tell us (by clicking in the circles below) how often you use the following resources to gather health information. Please click on ONLY one circle for each item.

<table>
<thead>
<tr>
<th>Resources</th>
<th>Always</th>
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<td>TV/Movies</td>
<td>jn</td>
<td>jn</td>
<td>jn</td>
</tr>
</tbody>
</table>

You have now completed the survey. Thank you for taking the time to assist us with this study.
INTRODUCTION
You have been asked to participate in a clinical trial, a type of research study, for a new medication that treats hypertension (high blood pressure). Clinical trials only include people who choose to participate. Before you agree to participate in this research study, it is important that you read and understand the following explanation of the study and the scheduled procedures. You may want to discuss your decision with family, friends or your doctor.

WHAT IS THE PURPOSE OF THIS STUDY?
This research study will test the safety and effects (good and bad) of a new drug that lowers blood pressure. The new drug, Lomycin, is investigational. In other words, this drug is currently not approved for the treatment of high blood pressure outside of this trial. People who enter into the study will take either the new drug, Lomycin, or Hydrozide. Hydrozide is an approved drug that most people currently take to lower their blood pressure. You are being asked to participate in this study because your blood pressure is currently not under control.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 700 participants will be enrolled onto this study.
WHO IS THE SPONSORING THE STUDY?

The study is sponsored by Pharma X. Your study doctor or hospital will be paid to cover the costs of your participation.

HOW DO I KNOW IF I AM ABLE TO TAKE PART IN THIS STUDY?

The Screening Period: During the screening period we will find out if you meet the basic requirements needed to take part in this study. During this screening period all your current blood pressure medicines will be stopped for one month and you will be given pills called Placebos. A placebo does not contain any active medicine. The placebos might cause your blood pressure to rise. You will need to attend the clinic 3 times a week for 4 weeks. This will allow the study staff to closely watch your blood pressure for any changes. If your blood pressure does get too high then you will be given immediate treatment. After 4 weeks, if your blood pressure is in the required range then you will be entered onto the study. If your blood pressure is not in the range required for this study then you will not be entered onto the study but will receive standard care for your blood pressure.

TREATMENT GROUPS

If the results of the screening find that you are eligible to participate in the study then you will be Randomised into 1 of 2 treatment groups. Randomisation means that you are put into a treatment group by chance (like a flip of a coin). Neither you nor the study doctor can choose the group you will be placed in. A computer program will randomly assign you to one of the following groups:

- **Group A:** If you are assigned to Group A you will receive Lomycin (investigational drug)
- **Group B:** If you are assigned to Group B you will receive Hydrozide (approved drug for the treatment of high blood pressure).

This is a Double Blind Study. This means that both you and your doctor will NOT KNOW which treatment group (Group A or Group B) you have been placed into. But, if this information is needed, it is available.
STUDY PROCEDURES (Both Group A and Group B)
You will be asked to come back to the clinic once a week for 20 weeks. At each visit you will be asked if you have had any bad reactions to the drug. As well, the following procedures will be conducted during each clinic visit:

- blood tests
- urine tests
- weight measures
- resting electrocardiogram (ECG which measures the electrical activity of the heart)
- blood pressure assessment

PATIENT RESPONSABILITIES
As a participant in this study you are responsible for completing the following tasks:

- Attend office visits
- Take your study medication every day as directed by the study doctor

**You must inform the study doctor if you:**

- Have a history of heart disease
- Are taking any other medication or plan to take any other medication. This includes prescription and non-prescription medications, herbal remedies and/or alternative therapies.
- Or your partner becomes pregnant at any time during this study

HOW LONG WILL I BE IN THE STUDY?
Your participation in the study may last up to 25 weeks. This includes the time spent during the screening period.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT
You may experience some side effects while participating in this study. Yet, doctors do not know all the side effects that may occur. Side effects may be mild or very serious. For your safety, the study doctor will review your past medical history and closely monitor you and your health during the study. You may be asked to stop being in the study if the doctor has concerns about your health. If you are asked to stop the study, the study doctor will continue
to monitor you until the condition or test results go back to normal. Some known side effects that may result from taking part in this study are listed in the table below.

**POTENTIAL SIDE EFFECTS**

<table>
<thead>
<tr>
<th>Side Effects of Lomycin</th>
<th>Side Effects of Hydrozide</th>
<th>Side Effects of Drawing Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Headaches</td>
<td>• Low blood potassium</td>
<td>• Fainting,</td>
</tr>
<tr>
<td>• Feeling drowsy</td>
<td>• A rise in blood uric acid &amp; blood sugar</td>
<td>• Swollen or sore veins</td>
</tr>
<tr>
<td>• Feeling tired or fatigued</td>
<td>• A lowering of red &amp; white blood cells</td>
<td>• Pain, bruising, bleeding at the site of the needle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Small risk of infection</td>
</tr>
</tbody>
</table>

**INFORMATION FOR WOMEN OF CHILDBEARING POTENTIAL**

We do not know if the study drug will affect mother's milk or an unborn fetus. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. If you are pregnant or become pregnant, there may be risks to the embryo or fetus that are unknown at this time. Women who can become pregnant must take a pregnancy test before the start of the study. Unless you cannot have children because of surgery or other medical reasons, you must have been using an effective form of birth control before you start the study. You must also agree to continue to use an effective form of birth control for 6 months after taking the study drug. Effective birth control methods include:

- birth control pills,
- patch,
- IUD,
- condom,
- sponge,
- diaphragm with spermicide,
- avoiding sexual activity that could cause you to become pregnant.
ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
By participating you will receive free hypertension treatment, including medication, for the entire length of the study. Doctors hope that Lomycin will improve your blood pressure but there is not proof of this yet. We do know that the results from this study will help doctors learn more about Lomycin as a treatment for high blood pressure. This information could help future patients with high blood pressure to better manage their condition.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?
You do not have to be in this study to get treatment for your high blood pressure. There are other approved medications available. Dr Smith will discuss which treatment options may be best for you.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?
YES. All data about you will be kept private. However, the following groups will be able to view and or copy your medical records:

- Authorize staff at Pharma X
- Members of health/medical authorities
- Ethics committees
- Other persons required by law may review the study data
- If you agree, your family doctor will be informed that you will be taking part in this study.

The results of this study may be published in scientific journals or presented at conferences for scientific purposes. These results could include your lab tests and X-rays. However, your identity will not be linked to any of the tests results.

WILL I BE TOLD ABOUT THE FINDINGS OF THIS STUDY?
YES. You will be told by your doctor or his staff if new information becomes available that might affect your decision to continue to participate in the study.

WILL I BE PAID FOR TAKING PART IN THIS STUDY?
NO. You will not receive any direct payment for participating in this study.
ARE THERE COSTS WITH TAKING PART IN THIS STUDY?

NO. There will be no charge to you for taking part in this study including office visits, medical exams and medication. As well you may be reimbursed for the cost of travel for your office visits if they become too costly. You should discuss any travel issues with the study doctor or staff.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY

You should tell the study doctor right away if you feel you have been injured because of taking part in this study. The sponsor of the study will pay for the treatment of injury that is a direct result of the study drug or study tests. You DO NOT give up any legal rights for injury payment by signing this consent form.

CAN I STOP BEING IN THE STUDY?

YES. Taking part in this study is your choice. There will not be a penalty if you decide not to participate in this study. If you decide not to be in the study, you will not lose any health benefits or health care. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this clinic. If you do decide to stop taking part in the study, you will be asked to go to a final office visit. During this visit your study doctor will tell you how to stop taking the medication safely and discuss other treatment options with you.

As well, the study doctor or Pharma X may remove you from this study at any time with out your consent for the following reasons:

- An event or health condition places your health at risk
- You have not been following the study procedures/requirements
- The sponsor ends the study
- Any other valid reasons
WHO CAN ANSWER MY QUESTION ABOUT THE STUDY?

You can talk to Dr. Smith about any question or concerns you have about this study at 00 1111 2222.

This study has been reviewed by the Human Research Ethics Committee (HREC). If you have any concerns or complaints about the way in which the research is or has been conducted or questions about your rights then please contact the Complaints officer HREC, on 22 4444 5555.

If you seek emergency care, or if hospitalization is required, please let the treating doctor know that you are enrolled in a research study being conducted by Dr. Smith.

Thank you for taking the time to read this information sheet
CONSENT FORM

I _______________(insert name)__________________have been given the details about the research study. I have been given information about the known side effects and possible risks of the study drug. I have also been told about study procedures that I may receive.

I am free to accept or refuse to take part in this research study. I can stop taking part in the study at any time without giving a reason. If I do decide to stop taking part in the study it will NOT have an affect on my treatment. I will not lose my rights to treatment. I will also be offered other types of treatment if I choose to stop taking part of the study.

I agree that the data collected for this study will be used as stated. I realize that Pharma X may need to review the research data. My data will not have my name on it or any other information that would link the data back to me.

I agree that access to my health records may be given to authorized people at Pharma X and national/international authorities. My health records and / or study notes may need to be reviewed by study staff at sites other than the sites that I attend. I agree to this process.

I will not lose any rights that I have under local law by signing this form.

I have read and understand the information given to me in this informed consent form. I have been given the option to ask questions. All of my questions have been answered. I may contact Dr. J Smith if I have any more questions about taking part in this study.

I will be given a signed and dated copy of this Informed Consent Form.

________________________  __________________________  __________________________
Print Name of Patient          Date                      Signature

________________________  __________________________  __________________________
Print Name of Researcher       Date                      Signature
Informed Consent to Participate in a
Clinical Research Study

PARTICIPANT INFORMATION SHEET

TRIAL: D 000-000 01

PROTOCOL TITLE
A Phase III Double-blind Randomised trial to test the Safety and Efficacy of Lomycin vs. Hydrozide in the Treatment of Hypertension
Appendix G.3 Hypertension MICCA

1. True/False Questions

Instructions: Please click on the circle that best answers each statement listed below. You may ONLY CLICK ON ONE circle for each statement.

1. The clinical trial is a form of research.
   - True
   - False
   - I don't know

2. I am required to take part in the clinical trial.
   - True
   - False
   - I don't know

3. I have been told who is funding the clinical trial.
   - True
   - False
   - I don't know

4. I have been told the total number of people that will take part in the clinical trial.
   - True
   - False
   - I don't know

5. During the clinical trial I will know which treatment I am receiving.
   - True
   - False
   - I don't know

6. During the clinical trial the study doctors will know which treatment I am receiving.
   - True
   - False
   - I don't know

7. During the clinical trial no one will be allowed to see my health information.
   - True
   - False
   - I don't know
Appendix G.3 Hypertension MICCA

8. I will be told about new findings from the clinical trial so I can decide whether to continue to take part.
   - True
   - False
   - I don't know

9. I have been told who will pay for my treatment if I become ill or injured as a result of the clinical trial.
   - True
   - False
   - I don't know

10. I have been given the name and phone number of the person to contact if I have questions or concerns about the clinical trial.
    - True
    - False
    - I don't know

11. My participation in the clinical trial can be stopped without my consent.
    - True
    - False
    - I don't know

12. I will be asked to pay for costs related to taking part in the clinical trial.
    - True
    - False
    - I don't know

13. I will be paid for taking part in the clinical trial.
    - True
    - False
    - I don't know
Instructions: Please click on the circle that best answers each question listed below. You may ONLY CLICK ON ONE circle for each statement.

14. How will it be decided which treatment group you will be placed into?
   - jn The group I am placed into will be based on my health care needs
   - jn The group I am placed into will be randomly assigned to me
   - jn I am free to decide which group I would like to be placed into
   - jn I don’t know

15. The clinical trial includes a treatment that has not been approved for your condition. What does this mean?
   - jn Outside of this trial, the treatment CAN be used for people with my condition
   - jn Outside of this trial, the treatment CANNOT be used for people with my condition
   - jn The treatment is the best possible for my condition
   - jn I don’t know

16. How long can you expect to be in the clinical trial?
   - jn 5 weeks
   - jn 25 weeks
   - jn 75 weeks
   - jn I don’t know

17. At what point can you leave the clinical trial?
   - jn I can leave at any time
   - jn I can only leave once the study is over
   - jn I can only leave once all of my data has been collected
   - jn I don’t know

18. What does it mean when you sign the clinical trial consent form?
   - jn I would like to take part in other similar trials
   - jn I do NOT want to take part in this trial
   - jn I am agreeing to take part in this trial
   - jn I don’t know
3. Check Boxes

Instructions: Please click on the box or boxes that best answers each question listed below. You may click on MORE THEN ONE box for each question.

19. Which describes the main purpose(s) of the clinical trial?
   - To identify how well the treatment works
   - To identify how much of the treatment can be given without causing harm
   - To improve my own medical/health condition
   - To test the safety of the treatment
   - I don't know

20. Which procedure(s) will you be asked to take part in?
   - Blood collection
   - ECG reading
   - Body measures (height, weight etc)
   - Urine collection
   - I don't know

21. Which task(s) will you be asked to complete?
   - Attend scheduled office/clinic visits
   - Follow a specific diet
   - Inform study doctors before taking prescription or non-prescription drugs (including herbal remedies)
   - Inform study doctors if you or your partner becomes pregnant
   - I don't know

22. Which side effect(s) might occur?
   - Fatigue
   - Headaches
   - Low blood potassium
   - Low red & white blood cell count
   - I don't know
23. Which describes the main benefit(s) that may result from taking part in the clinical trial?

- Finding treatment(s) that may help others that have my condition
- Free medical care
- Free health/medical education
- Cure or improve my own health/medical condition
- I don't know

24. Which describes the other treatment option(s) available to you?

- Drug treatment (prescription or non-prescription)
- Radiation treatment
- Surgical treatment
- There are NO other treatment options available
- I don't know
## 4. About You

Instructions: Please tell us about yourself by clicking on the circle that best answers each question listed below. You may ONLY CLICK ON ONE circle for each statement.

### 25. How old are you?

- [ ] Younger than 40
- [ ] 40-49
- [ ] 50-59
- [ ] 60-69
- [ ] 70+

### 26. Where do you live?

- [ ] Australia
- [ ] Canada
- [ ] New Zealand
- [ ] United Kingdom
- [ ] United States
- [ ] Other

### 27. What is your gender?

- [ ] Male
- [ ] Female

### 28. Which best describes your background?

- [ ] Aboriginal/Torres Strait Islander
- [ ] African American
- [ ] Asian
- [ ] Caucasian
- [ ] Latino
- [ ] Maori
- [ ] Pacific Islander
- [ ] Other
Appendix G.3 Hypertension MICCA

29. Which describes the highest level of education you have completed?

- Primary school
- Secondary school
- Technical/vocational education
- Some university education
- Completed an undergraduate degree
- Completed a higher graduate degree (Masters, PhD etc.)

30. Have you ever taken part in a clinical trial?

- Yes
- No
- I don’t know

31. Please tell us (by clicking in the circles below) how often you use the following resources to gather health information. Please click on ONLY one circle for each item.

<table>
<thead>
<tr>
<th>Resource</th>
<th>Always</th>
<th>Sometimes</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Books/Journals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friends/Family</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health care provider (Drs, nurses etc)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internet</td>
<td></td>
<td></td>
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<tr>
<td>Popular magazines</td>
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<td></td>
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<tr>
<td>Radio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TV/Movies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

You have now completed the survey. Thank you for taking the time to assist us with this study.