

https://dspace.org/

Informed consent methods: an analysis of volunteer understanding

Jacobs, Janine

2009-02-26T08:14:52Z
http://hdl.handle.net/10539/6494

Downloaded from a DSpace repository. https://dspace.org/

INFORMED CONSENT METHODS: AN ANALYSIS OF VOLUNTEER UNDERSTANDING

Janine Jacobs
0491763Y
University of the Witwatersrand

A Research Report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements of the degree Master of Science in Medicine in Pharmaceutical Affairs.

2008

DECLARATION

I, Janine Jacobs, declare that this dissertation is my own, unaided work. It is being submitted for the degree of Master of Science in Medicine in the branch of Pharmaceutical Affairs at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signature of Student:

Janine Jacobs	Date

I certify that the studies contained in this dissertation have the approval of the following ethics committee's:

- University of the Freestate, reference number: ETOVS NR 178/06
- University of the Witwatersrand, reference number: M070529

Signature of Student:

Janine Jacobs	Date

Signature of Supervisor:

Dr. Gareth Lowndes	Date

COPYRIGHT

Attention is drawn to the fact that copyright of this research report rests with its author. This copy of the research report has been supplied on condition that anyone who consults it is understood to recognize that its copyright rests with its author and that no quotation from the research report and no information derived from it may be published without prior written consent of the author.

To my father

The late Dr. P.C. Jacobs,

For giving me the wings to fly

To my mother

Isabel,

For making me believe that I can achieve anything I put my mind to

ABSTRACT

To develop a more efficient way of informing potential clinical trial volunteers of exactly what they could expect during (and after) their participation in a clinical trial as well as the sponsor's expectations from the volunteer.

A multiple choice questionnaire, which was based on the criteria as specified by Guideline 5 of the International Conference of Harmonization (ICH), was administered to 28 Volunteers after only reading the Patient Information Leaflet/Informed Consent Document (PIL/PIL/ICD), to 21 Volunteers who had read the PIL/ICD and attended a question and answer session, to 17 Volunteers who had read the PIL/ICD and attended a presentation and 19 Volunteers who had read the PIL/ICD and attended a presentation and a question and answer session. In total, 85 Volunteers completed the questionnaire.

The average calculated percentage* of volunteers who had only read the PIL/ICD was 61%, 63% for Volunteers who had read the PIL/ICD and attended a question and answer session, 73% for Volunteers who had read the PIL/ICD and attended a presentation and 68% for Volunteers who had read the PIL/ICD and attended a presentation and question and answer session. In total, the average calculated percentage was 66%. Eighty four percent of the total number of volunteers answered the question on withdrawal consequence incorrectly, 43% of Volunteers answered questions on side effects incorrectly and 100% of the Volunteers answered the question on the duration of storage of samples incorrectly.

Despite increasing regulatory and ethical scrutiny, deficiencies still exist in Volunteer comprehension of the research in which they participate, as well as differences in how comprehension is measured and assessed. Results indicated that any successful consent process should, at a minimum, include a visual communication mode. Concepts that are not well understood within the South-African context are withdrawal consequence, methodology such as double-blind or single blind, side effects, duration of archiving, treatment alternatives and the role of the investigator.

**calculated % for each volunteer = score out of 25 x 100*

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dr. G.J. Lowndes (University of the Witwatersrand, Department of Pharmacy) for his guidance, critical review and most importantly, his patience. Without his support, this project would not have been possible.

A special thanks to Ronelle van Niekerk for her invaluable critique and statistical review of this project.

I would also like to thank the following members of staff at the FARMOVS/Parexel clinic in Bloemfontein who made this project possible:

- Dr. Sybrand Pretorius
- Dr. Gerhard Groenewoud
- Dr. Johann Terblanche
- Sr. Lettie Rehne
- Dr. Mada Ferreira
- Dr. Arnelle Mostert
- Ilse Reblin
- Hennie Trollip

Lastly, I would like to thank Cynthia Cowie for the grammatical review of this dissertation and for always lending an understanding ear and unwavering support.

ABBREVIATIONS

ADR	Adverse Drug Reaction
CIOMS	Council form International Organizations of Medical Sciences
EMEA	European Medicines Agency
IC	Informed Consent
ICD	Informed Consent Document
PIL/ICD	Patient Information Leaflet/ Informed Consent Document
ICH	International Conference of Harmonization
ICU	Intensive Care Unit
PIL	Patient Information Leaflet
SOP	Standard Operating Procedure

DEFINITIONS

Investigator	1.) One or more persons responsible for the practical performance of a trial and for the integrity, health, and welfare of the subjects during the clinical study. The individual(s) who actually conducts the clinical investigation and under whose immediate direction drug is administered or dispersed to a subject. 2.) A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
PIL/ ICD (Patient Information Leaflet/ Informed Consent Document)	The form prepared by the investigator and/or the sponsor, and approved by the Independent Ethics Committee, which must be signed by the subject before entry in a clinical trial. It is the legal written record that the subject, or his/her representative, agrees to voluntarily participate in the investigation. Also referred to as "consent form" or "subject consent form".
Vulnerable Population	Any circumstances in which volunteers are in a position of dependency (research volunteers, elderly, indigenous, poor people, illiterate people, dying volunteers) make them potentially vulnerable [15]

TABLE OF CONTENTS

		Page
Declaration		ii
Dedication		iv
Abstract		v
Acknowledgements		vi
Abbreviations and Definitions		vii
Chapter 1: Introduction		
1.1	Introduction	1
1.2	Prior Studies	5
1.3	Definition of "Informed Consent"	8
1.4	Steps to obtain Informed Consent	9
1.5	Legal Issues	10
Chapter 2: Study Objectives		
2.1	Aim	12
2.2	Objectives	12
2.3	Procedure	12
2.4	Informed Consent for this Project	14
2.5	Questionnaire	15
2.6	Presentation	21
2.7	Recruitment	22
Chapter 3: Results		
3.1	Results	23
3.1.1	Objective 1: Compare the efficiency of data transfer to volunteers enrolled on a clinical trial by assessing their comprehension of clinical trial concepts	23
3.1.1.1	Categorical Variables	24
3.1.1.2	Continuous Variables	30
3.1.1.3	Number of Questions Answered Correctly	31
3.1.2	Objective 2: Identifying the Most Effective PIL/ICD Method	33
Chapter 4: Data Analysis and Discussion		
4.1	Data Analysis and Discussion	35
4.1.1	Comprehension of Clinical Trial Concepts	36
4.1.1.1	Voluntary Participation	37
4.1.1.2	Compensation	37
4.1.1.3	Withdrawal Consequence	38
4.1.1.4	Study *versus* Treatment	39
4.1.1.5	Study Methodology	39
4.1.1.6	Side Effects	40
4.1.1.7	Volunteer Protection	41

4.1.2 Method of Data Transfer 41

Chapter 5: Conclusion & Recommendations
5.1 Limitations 43
5.2 Conclusions and Recommendations 44

LIST OF FIGURES

Figure 1: Volunteer Comprehension: Percent of Study Volunteers 3
Figure 2: Volunteer Understanding of Study Design: Percent of Study Volunteers 3
Figure 3: Intensive Care Unit Study Results 6
Figure 4: Methods of Data Transfer 13
Figure 5: Example: Masking of Correct Answer 16
Figure 6: Number of Questionnaires Collected 23
Figure 7: Frequency Distribution of Number of Correct Answers (n=85) 32
Figure 8: Frequency Distribution of Number of Correct Answer by PIL/ICD Method 32
Figure 9: Voluntary Participation 37
Figure 10: Compensation 38
Figure 11: Withdrawal Consequence 38
Figure 12: Study Versus Treatment 39
Figure 13: Study Methodology 40
Figure 14: Side Effects 40
Figure 15: Volunteer Protection 41

LIST OF TABLES

Table 1: Categorical Variables by Group 24
Table 2: Continuous Variables by Group 30
Table 3: Number of Questions Answered Correctly by Group 31
Table 4: Calculated Mark (number of questions answered correctly) 33
Table 5: Calculated Mark % ((calculated mark/25)*100) 34
Table 6: Ranking of questions in order of number of correct answers 36

REFERENCES 47

LIST OF APPENDICES

APPENDIX I: Obtaining Informed Consent: Essential Information 49
APPENDIX II: Presentation 52
APPENDIX III: Study Specific Informed Consent Document 71
APPENDIX IV: WHEC Approval 79
APPENDIX V: UOFS Ethics Committee Approval 80

CHAPTER 1: INTRODUCTION

1.1 Introduction

Following the TeGenero (TGN 1412) Phase I trial in April 2006 where six volunteers nearly died due to unexpected Adverse Drug Reactions (ADR), the informed consent (IC) process received renewed attention.

Volunteers claimed that they where not aware of the potential danger of the trial despite an elaborate IC process. The volunteers claimed that the IC process was not thorough enough and was performed in haste. Investigations into the matter proved the contrary and that the staff that administered the IC was not at fault.

This raises the question: How informed are volunteers?

Nirmala Bhogal, science manager at the Fund for the Replacement of Animals in Medical Experiments, argues that people will now be more demanding about the data they are given before they take part in trials. *"Healthy people will probably now be unwilling to volunteer unless they are given more information,"* she says. *"Perhaps volunteers should be shown all the available data and allowed to make their own judgments"* [1].

Regardless of the potential risks and dangers of clinical trials, they are still essential for the progress of medicine.

In recent years there has been a shift in thinking by volunteers and professionals alike: volunteers should be involved in decisions about their own care. However, we have not yet seen a change in volunteer's involvement as proven by numerous studies mentioned below. Volunteers still rely on their healthcare providers to provide the "best" care without paying much attention to what they are being told, and thus, placing their trust in their healthcare providers during the decision making process.

A major concern is that the medical research being conducted in third world countries is often sponsored by first world countries. South-Africa is particularly attractive for

clinical research because of a large population, modern medical facilities and low per capita income. This necessitates the need for a valid informed consent.

Although it is clear that there are warning signs regarding volunteer's comprehension in both "developed" and "developing" communities in South-Africa, there has been very little investigation conducted into how to actually address this problem.

Furthermore, there is often a great difference between the readability of the PIL/ICD and the volunteers' understanding of it. Although the volunteer's understanding and recall of the words used may be readily tested, comprehension of the concepts involved (e.g. benefit-to-risk ratio) are difficult to measure even in controlled settings [2].

In an online survey conducted by CenterWatch in January & February of 2002, a surprising amount of volunteers (14%, n=1561) reported that they had signed the Informed Consent without even reading the form. *"The form was Greek to me; and no one really explained anything. They handed me the papers and gave me a lot of time to look them over. I just asked a few questions, then went ahead and signed it. I didn't worry because I knew that I could pull out of the study at any time. I felt safe enough"*[3].

Another volunteer disagreed: *"Study staff wanted to make sure I knew exactly what the terms in the form meant. They explained everything very well and told me about the risks and side effects. They kept reminding me that if I had any questions I could call them at any time"* [3].

The majority of volunteers (86%) indicated that they had read the Informed Consent prior to signing it.

The following results were found regarding volunteer comprehension & understanding of study design [3]:

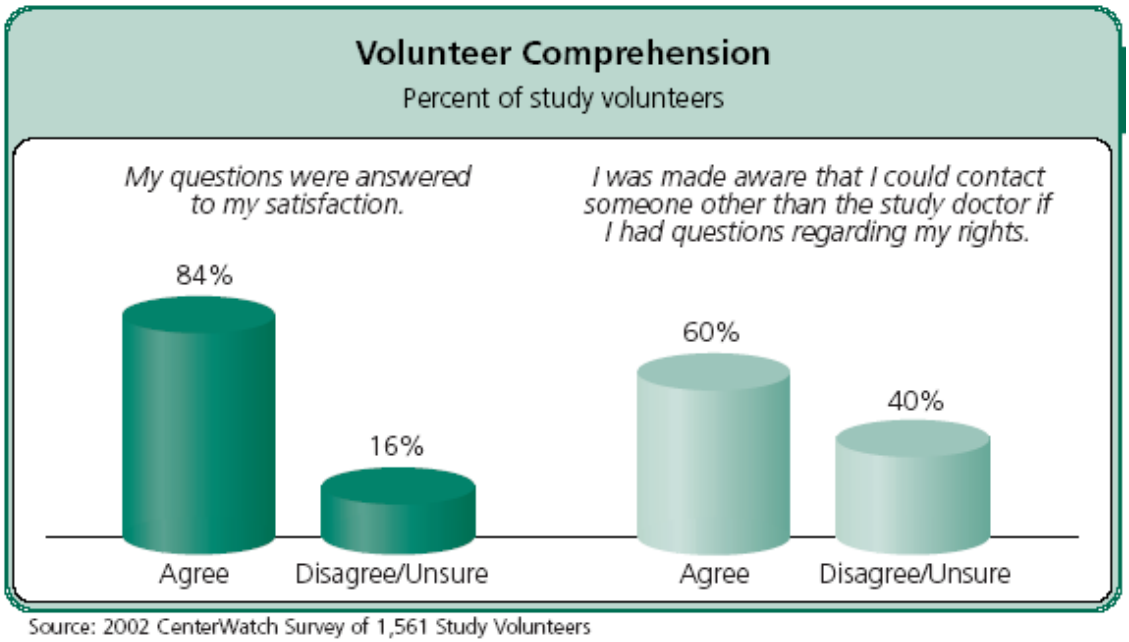


Figure 1: Volunteer Comprehension: percent of study volunteers

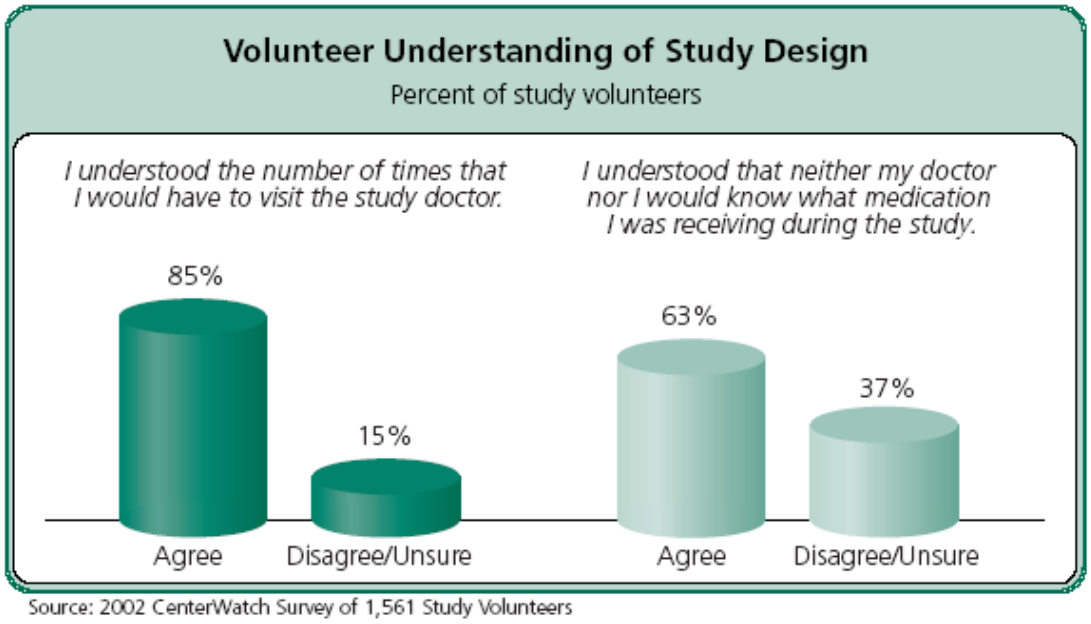


Figure 2: Volunteer Understanding of Study Design: percent of study volunteers

Numerous guidelines have been developed in recent years on exactly what information should be shared with prospective volunteers in clinical trials. These include local requirements as well as global recommendations. Globally, the "Gold Standard"

guidelines are provided by the *Declaration of Helsinki (2003)* and the International Conference of Harmonization (ICH).

The *Declaration of Helsinki* requires the following information to be disclosed within the PIL/ICD:

- The study's aims and methods
- Sources of funding and possible conflict of interests
- The researcher's institutional affiliations
- Anticipated benefits and potential risks and the follow-up of the study
- Discomfort that trial participation may entail
- Right to abstain from participation in the study, or withdraw from it at any time without any reprisals (World Medical Association. *Declaration of Helsinki*. 2003)

Bert Spilker has recommended the following methods to increase the level of a volunteer's comprehension about a clinical trial[2]:

A. Writing the PIL/ ICD

1. Use words of one or two syllables whenever possible
2. Use short declarative sentences
3. Avoid legal phases
4. Follow a format that leads the volunteer logically through all parts of the clinical trial
5. Explain scientific terms and words in lay language (e.g. "test to look at brainwaves" instead of EEG[2].

B. Evaluating the PIL/ ICD

1. Assess the readability with a standard scale (e.g. Flesch Fry)
2. Assess the comprehension by having nontrial volunteers read and critique the PIL/ ICD
3. Assess connotations of words used to ensure that volunteers are not

mislead[2]

C. Counseling the volunteer

1. Review the overall nature of the clinical trial with each volunteer before they read the form
2. Have group question-and-answer sessions of several volunteers and supply background information
3. Have the volunteers keep the form for at least 12-24 hours before they are requested to sign
4. Repeat some or all aspects of the informed consent procedure during the trial
5. Have another volunteer advocate clarify issues with the volunteer[2]

D. Other

1. Provide counseling to the volunteer's family
2. Divide the process into two parts, by which the second is done on a different day and confirms that the volunteer still desires (or is willing) to enroll and has no further questions
3. Have the volunteer explain to the investigator or another person to verify that the volunteer understands the nature of the clinical trial[2]

1.2 Prior Studies

Several studies conducted in both Europe and North America have assessed the degree of comprehension of the informed consent process, and have illustrated flaws in comprehension [4].

In a study [5] to analyze the procedure of informed consent for Intensive Care Unit (ICU) research obtained before ICU admission showed that as many as 22% of ICU volunteers who consented to participate in a study were unable to recall their participation in the study, although they had provided their consent prior to their admission, in a non-stressful environment (prior to elective admission).

The results of this study [5] can be summarized as follows:

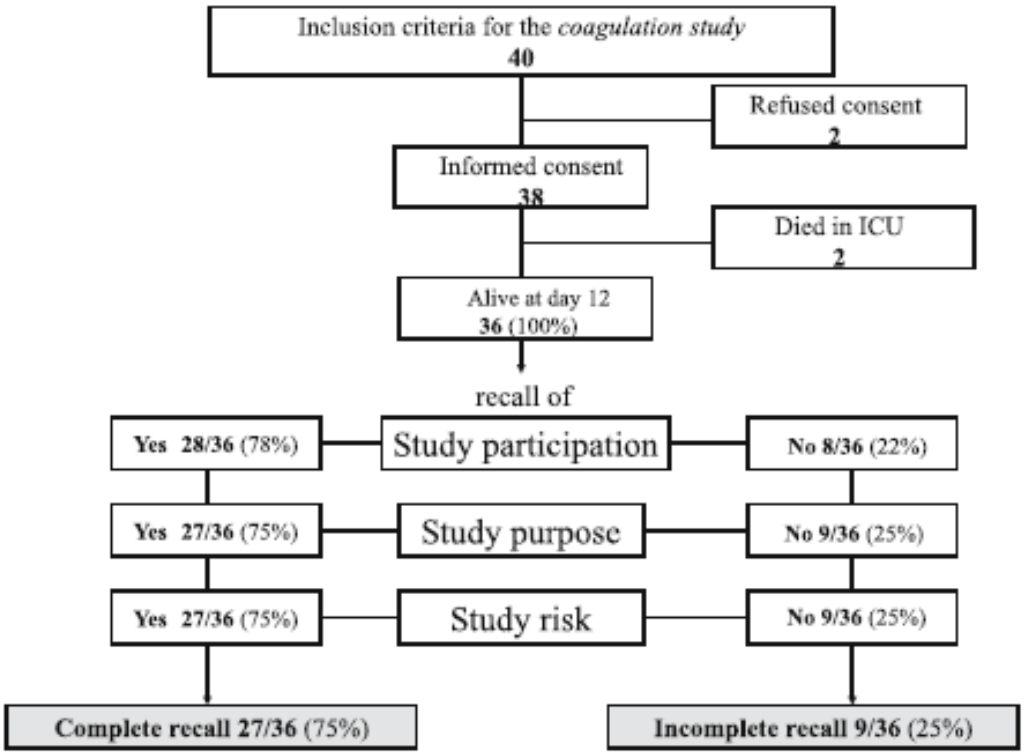


Figure 3: Intensive Care Unit study results[5]

Among consenting parents in nine European countries 20.7% of parents misunderstood the concept of voluntary withdrawal [6]. A qualitative study in East Africa revealed common themes such as *"…it is inappropriate to question a doctor"*, and *"…there are no risks to this study"* amongst consenting volunteers [7].

As a part of a study on the desired features in multimedia consent forms, Jamison *et.al.*[14] asked 29 volunteers with potential cognitive impairments (depression, schizophrenia and breast cancer) to read a sample consent form and to suggest improvements to that form. These volunteers said that the consent form was too long, with too many complex words and confusing details. One must thus be aware that retention of information may be compromised by information overload.

The most insightful study regarding volunteer comprehension was conducted quite recently in Mali, West Africa by Krosin *et.al*. 2006[8] whereby a questionnaire containing nine questions was administered to assess volunteer comprehension regarding the following topics:

1. Voluntary participation
2. Compensation
3. Withdrawal criteria
4. Withdrawal consequence
5. Study versus treatment
6. Study administration
7. Randomization and placebo
8. Side effects
9. Lay scientific knowledge[8]

These questionnaires were administered to 163 rural and peri-urban volunteers. The results are as follows:

- 43% answered the question on voluntary participation incorrectly
- 56% answered the question on compensation incorrectly
- 90% answered the question on withdrawal criteria incorrectly
- 56% answered the question on withdrawal consequence incorrectly
- 74% answered the question on study *versus* treatment incorrectly
- 34% answered the question on study administration incorrectly
- 32% answered the question on randomization and placebo incorrectly
- 93% answered the question on side effects incorrectly (which bears critical ethical consequence)
- 27% answered the question on lay scientific knowledge incorrectly

Although these results are poor, it is likely that the percentages of correct answers observed are high relative to the population sampled. Thirty seven percent of the study population could not reliably use a multiple choice format and were ineligible for the survey [8].

The results of the above study should be viewed in context with other studies conducted in the industrialized world.

In another study, 156 war veterans were interviewed to determine their degree of understanding of a clinical protocol for which they had signed a PIL/ICD. They were interviewed less than 10 weeks after signing: only 10% could totally describe the objective of the study [9].

There are no studies available in South-Africa on how to improve the PIL/ICD process.

1.3 Definition of "Informed Consent"

Informed consent is defined by the International Conference and Harmonization[11] as:

"*The process by which a volunteer voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all the aspects of the trial that are relevant to the volunteer's decision to participate. Informed Consent is documented by means of a written, signed and dated PIL/ICD*" [11].

Informed consent is a decision to participate in research, taken by a competent volunteer who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been volunteered to coercion, undue influence or inducement, or intimidation[10].

Informed consent is based on the principle that competent volunteers are entitled to choose freely whether to participate in research. Informed consent protects the volunteer's freedom of choice and respects the volunteer's autonomy. As an additional safeguard, it must always be complemented by independent ethical review of research proposals. This safeguard of independent review is particularly important as many volunteers are limited in their capacity to give adequate informed consent; they include young children, adults with severe mental or behavioral disorders, and persons who are unfamiliar with medical concepts and technology[10].

Obtaining informed consent is a process that is begun when initial contact is made with a prospective volunteer and continues throughout the course of the study. By informing the prospective volunteers**,** by repetition and explanation, by answering their questions as they arise, and by ensuring that each volunteer understands each procedure, investigators elicit their informed consent and in so doing manifest respect for their dignity and autonomy. Each volunteer must be given as much time as is needed to reach a decision, including time for consultation with family members or others. Adequate time and resources should be set aside for informed-consent procedures[10].

The investigator must then ensure that the prospective volunteer has adequately understood the information. The investigator should give each one full opportunity to ask questions and should answer them honestly, promptly and completely. In some instances the investigator may administer an oral or a written test or otherwise determine whether the information has been adequately understood [4].

1.4 Steps to obtain informed consent

There are several key elements of the IC process which requires the research team to share open and honest information regarding the clinical trial which in turn, can be easily understood by the volunteer and allows him/her to act upon this information[10].

Firstly, the research team has to provide **transparent information** in such a way that it can be easily understood. Aspects such as the nature of the sponsorship, benefits and risks of participation, and the responsibility for care and complications must be carefully explained. The volunteers must be given the opportunity to ask questions in order to clear ambiguities and obtain additional information[10].

The second step is critically important: the volunteer must understand what is asked of them [10].

Lastly, the volunteer must freely agree to take part in the clinical trial. Therefore, not only must the volunteer understand the project but must be competent to give consent or decide to withdraw [10].

In conclusion, the cases above highlight that the process of informing volunteers of potential risks and benefits related to their participation in a clinical trial, is proving to be a difficult art to master.

1.5 Legal Issues

USA Today reported last year that the pharmaceutical industry *"…faced the most product liability lawsuits of any other industry"* [18].

Lawsuits against pharmaceutical companies totaled 17 027 last year, more than all other industries with significant liability suits combined: n = 3 236 (Manufacturing); n = 2 875 (Chemicals); n = 2 717 (Construction); n = 2 636 (Financial services) and n = 1 926 (Insurance) [18].

Recent years have seen an increase in lawsuits where the validity of the informed consent process has been questioned and in many cases found invalid.

In the most recent case, Kano State Government versus Pfizer, 5 children died after they received an experimental drug named Trovan® for meningococcal meningitis, although there is no indication in the documents that the drug caused the deaths. Six children died after receiving the comparator drug, Hoffmann-La Roche's Rocephin® (ceftriaxone). It was found that there were no consent forms (many parents of the children were illiterate) and no signatures from witnesses to confirm that parents understood that their children were taking part in an experiment. In fact, in certain reports it was stated that the parents were banned from entering the wards where their children were being treated. This trial is still ongoing.

Another common theme amongst recent lawsuits is the failure to disclose conflict of interest. In the case of Jesse Gelsinger *versus* Genovo [17], it was discovered that Dr Wilson (the Principal Investigator) owned 30% of the shares in Genovo.

There are many more examples of lawsuits that have been concluded in favour of the plaintiff due to insufficiencies within the informed consent process or documents. Thus to ensure the protection of volunteers and that valuable research is not lost, more time should be invested into the improvement of this vital component of clinical research.

Since there is an increased legal awareness of the validity of the Informed Consent process and documentation as seen in the Kano State Government *versus* Pfizer, it is imperative to ensure that this process is both ethical and legal.

CHAPTER 2: STUDY OBJECTIVES

2.1 Aim

The aim of this project was to develop an efficient method of informing potential clinical trial volunteers of exactly what they could experience during (and after) their participation in a clinical trial.

2.2 Objectives

(i) To compare the efficiency of data transfer to volunteers enrolled on a clinical trial by assessing their comprehension of clinical trial concepts

(ii) To identify the most effective method of transferring data to volunteers intending to enroll into a clinical trial.

2.3 Procedure

Currently various methods are used to inform volunteers of the potential benefits and risks associated with their participation in a clinical trial (sometimes in various combinations):

- Volunteers are provided with a copy of the PIL/ICD to read the day prior to the actual Informed Consent session
- Group Question & Answer sessions
- In depth PIL/ICD discussions
- Presentations (although rarely used)

To ensure that various combinations of the above mentioned methods were tested, the questionnaires were administered at various time points during the Informed Consent procedure:

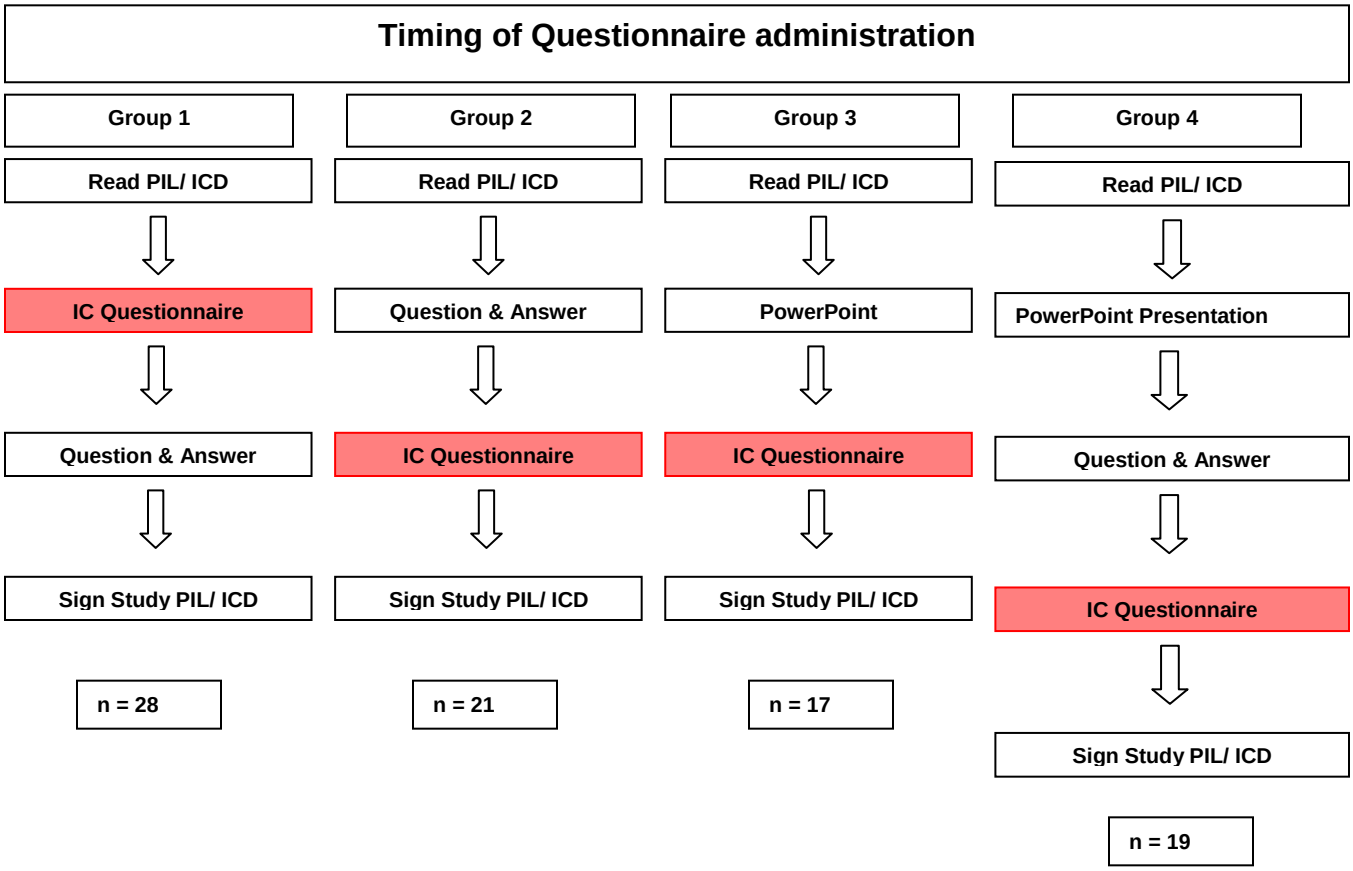


Figure 4: Methods of data transfer

There were four groups of volunteers:

- Group 1: volunteers who had only read the PIL/ICD
- Group 2: volunteers who had read the PIL/ICD and attended the group question & answer session
- Group 3: volunteers who had read the PIL/ICD and attended the presentation
- Group 4: volunteers who had read the PIL/ICD, attended the presentation & attended the group question & answer session

The four groups comprised out of volunteers participating in ***actual trials*** at the FARMOVS/PAREXEL facility during the last two years in the following indications:

- Group 1: Human Immunodeficiency Virus (HIV) and Asthma trials
- Group 2: Human Immunodeficiency Virus (HIV) and Asthma trials
- Group 3: Alcohol addiction trial

- Group 4: Human Immunodeficiency Virus (HIV) , Asthma and Alcohol addition trials

Due to logistical reasons it was not possible to distribute participants from these trials equally into each group. All procedures were standardized across the different trials.
Please refer to APPENDIX IV for an example of the PIL/ICD used for these trials.

Each volunteer was only allowed to participate once and be included into one group. Volunteers were assured that their participation was entirely voluntary and that the results of the questionnaire would be anonymised by assigning a questionnaire number only. No personal identifiers such as the volunteer's name or initials were noted. Volunteers were also assured that the results of the questionnaires did not affect their eligibility for the prospective trial they were being screened for.

Where a method of data transfer would normally be considered unethical such as only allowing a volunteer to read the PIL/ICD and then sign the consent form, the informed consent procedure was resumed after completion of the questionnaire.

For instance, volunteers in group 1 had the opportunity to read the PIL/ICD and were then asked to complete the questionnaire. Upon completion of the questionnaire, they would then attend a question and answer session and the informed consent procedure would be completed as per the standard operating procedure of FARMOVS/PAREXEL.

2.4 Informed Consent for this project

A PIL/ICD was developed for this project. However, it was decided not to obtain Informed Consent to partake in this project as it would have introduced bias and thus would have unduly influenced the outcome of this project. Volunteers were verbally invited by the study physician to complete the questionnaire. It was explained to the volunteers that their results would in no way affect their eligibility and that the results would merely be used to improve current practices and procedures.

The volunteers did, however, sign the actual clinical trial's screening and enrollment PIL/ICD's as *per* the specific trial sponsor's and FARMOVS/PAREXEL Standard Operating Procedures (SOP's). These were then filed together with all other study related documentation on site.

2.5 Questionnaire

Guideline 5 of the International Ethical Guidelines for Biomedical Research involving human volunteers specifies 26 distinct concepts which needs to be shared during the Informed Consent process (APPENDIX I).

A generic questionnaire was then developed based on ICH: Guideline 5 to test the volunteer's comprehension of these various concepts. These questionnaires were multiple choice with four possible responses to each question. Comprehension of the following concepts was tested:

1. Voluntary participation
2. Compensation
3. Withdrawal consequence
4. Study *versus* treatment
5. Study administration
6. Randomization and placebo (study methodology)
7. Side effects
8. Volunteer protection (maintaining volunteer anonymity)

Hochhauser *et.al.* 2004[13] pointed out that since multiple choice questions include the correct answer among the incorrect alternatives; they measure recognition, not recall. In this project, the problem was addressed by using the same term in different ways *e.g.:*

The purpose of this trial is to establish:

The difference between 4 Acamprosate calcium capsule products	If the product to be tested (Acamprosate calcium) is not safe	To prove that Acamprosate calcium is the best	To prove that Acamprosate needs to be used in conjunction with Besobrial
A ☐	B ☐	C ☐	D ☐

Figure 5: Example: masking of correct answer

Each questionnaire was then modified according to each specific trial based on the study specific PIL/ICD for the applicable trial and consisted out of 25 questions:

Informed Consent Questionnaire

Instructions:
This questionnaire is intended to establish your understanding of the clinical trial that you are enrolling in. It will NOT affect your eligibility to enroll into the study.
The questionnaire is anonymous- please DO NOT write your name (or any part of it) on the questionnaire
Please tick the correct answer with a "x"
Thank you for completing the questionnaire

DEMOGRAPHIC INFORMATION:

Questionnaire Number:

0001

Highest level of Education:

Primary school	High school	Tertiary education	Illiterate
☐	☐	☐	☐

Race:

Black	White	Coloured	Asian
☐	☐	☐	☐

Date of Birth:

Day (dd)	Month (mm)	Year (yy)

Gender:

Male	Female
☐	☐

1) Participation in this clinical trial is:

Required by the Medicines Control Council (MCC)	Voluntary	Required by the sponsoring company	Required by South-African government
☐	☐	☐	☐

2) If you withdraw from the clinical trial you will lose the following benefits you would otherwise be entitled to:

Partial compensation	All compensation	Follow-up care/visits	None
☐	☐	☐	☐

3) The purpose of this trial is to establish:

If the product to be tested (XXX) is the same as what is currently available on the market (XXX)	If the product to be tested (XXX) is not the same as what is currently available on the market (XXX)	To prove that (XXX) is the best	A & C
☐	☐	☐	☐

4) The following staff will know which volunteers has received either (XXX) or (XXX):

Clinic staff only	Laboratory staff only	Both clinic staff and Laboratory staff	Nobody
☐	☐	☐	☐

5) What is the duration of this study?

3 weeks (19 days)	6 weeks (40 days)	4 weeks (26 days)	8 weeks (53 days)
☐	☐	☐	☐

6) You will be compensated for your participation in the following way:

R1980	R1980 and petrol money	Food, drink and accommodation	None, participation is voluntary
☐	☐	☐	☐

7) After the trial:

You will have to read the newspaper to get the results	The results will be broadcasted on T.V.	You will be informed of all findings related to your individual case	You will be informed in writing about the results of the trial
☐	☐	☐	☐

8) You are entitled to:

Nothing- you have been paid	The right of free speech	The right of freedom of association	The right of access to your data
☐	☐	☐	☐

9) You may experience:

Vomiting	Headache	Ear Ache	Sedation, Drowsiness and a drugged feeling
☐	☐	☐	☐

10) As a result of your participation, you will: (any benefits)

Receive the newest care available	Not have access to a Doctor	Have a complete medical evaluation	A and C
☐	☐	☐	☐

11) As a result of this study:

(XXX) might be cured	The (XXX) will not deteriorate as quickly	The transmission of (XXX) may be stopped	A, B and C
☐	☐	☐	☐

12) After the study you will

Receive medication free of charge for three years	Be phoned to participate in the follow-up study	Follow-up investigations will be conducted within 72 hours	Not be able to contract (XXX)
☐	☐	☐	☐

13) Currently, the following alternative treatment is available for your condition:

Herbal medication	Physiotherapy	Following a specific diet	Surgery
☐	☐	☐	☐

14) Your privacy will be protected in the following way:

Your telephone number will not be recorded anywhere at all	Only your participant number will be used during analysis	No other staff (other than the trial staff) will have access to your personal details	B & C
☐	☐	☐	☐

15) Any personal results from this study

Will not be communicated to anybody without your permission	Will be communicated to your next of kin only	Will be communicated to your insurance company	Will be communicated to anybody who needs to know
☐	☐	☐	☐

16) This study is sponsored by:

GSK	Novartis CH	Aventis	(XXX) Limited
☐	☐	☐	☐

17) Any records/data collected from you during the course of this study will

Be made available for all follow-up studies as well	Will not be used for any other purpose other than this study	Will be used to develop training material	Will be used to collect national statistics
☐	☐	☐	☐

18) After the clinical trial, your biological samples (i.e. blood or urine) will be:

Stored for three years	Stored for 15 years	Destroyed	Returned to you
☐	☐	☐	☐

19) A commercial product will be developed from your biological sample:

True	False
☐	☐

20) The doctor involved in the study will be acting as:

Your physician	The Investigator	The Investigator and your physician	None
☐	☐	☐	☐

21) It is the investigator's responsibility to

Provide only (XXX) related care	Protect life and health	Protect, life, health and privacy	Protect, life, health, dignity and privacy
☐	☐	☐	☐

22) Should you experience any adverse effects due to your participation to this study, you will:

Receive medical care free of charge until you are healthy again	Have to pay for 10% of your medical care	Your medical aid will have to pay for your medical care	Receive nothing
☐	☐	☐	☐

23) Should you die or be disabled as a result of your participation in this study, your family or dependants will receive:

R100 000 from the Medicines Control Council (MCC)	No compensation	R10 000 from (XXX)	A & C
☐	☐	☐	☐

24) The right to compensation is legally guaranteed:

True	False
☐	☐

25) The protocol for this study has been approved by the Ethics Committee:

True	False
☐	☐

2.6 Presentation

Colourful, descriptive, visual presentations were developed and were based on both the PIL/ ICD for the respective studies as well as Guideline 5 of the International Ethical Guidelines for Biomedical Research involving human volunteers. The presentations

were standard across the clinical trials with modifications made as applicable to each trial (refer to APPENDIX III).

The presentations were facilitated by the trial physicians.

2.7 Recruitment

As the FARMOVS/Parexel clinic is situated on the campus grounds of the University of the Free state, volunteers at this clinic consist mainly of students attending the University. Volunteers with a different demographic composition (e.g. volunteers >40 years of age) do occasionally also participate in the clinical trials conducted at this site.

For the purposes of this project, all volunteers (regardless of age, level of education, race or gender) who were being screened for various trials at FARMOVS/Parexel were invited to participate.

CHAPTER 3: RESULTS

3.1 Results

In total, 85 volunteer records were evaluated during the statistical analysis process:

- Read PIL/ ICD only (Group 1): n = 28 (32.94%)
- Read PIL/ ICD and Q&A session (Group 2): n = 21 (24.71%)
- Read PIL/ ICD and presentation (Group 3): n = 17 (20.00%)
- Read PIL/ ICD, presentation and Q&A session (Group 4): n = 19 (22.35%).

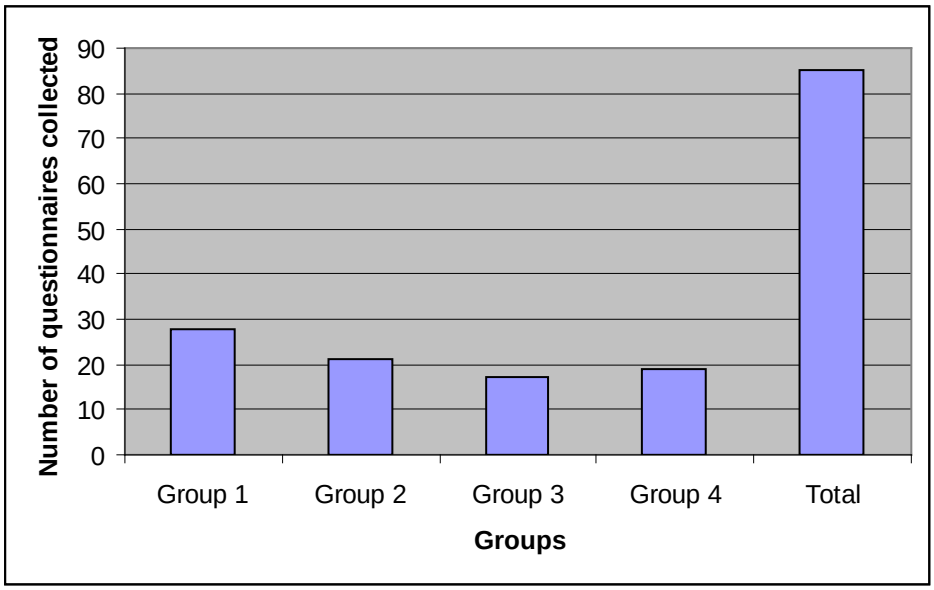


Figure 6: Number of questionnaires collected

3.1.1 Objective 1: Compare the efficiency of data transfer to volunteers enrolled on a clinical trial by assessing their comprehension of clinical trial concepts

The results of the volunteers that completed the questionnaire after participating in the protocols (group 1, 2, 3 and 4) can be summarized as follows:

3.1.1.1 Categorical Variables

Table 1: Categorical Variables by Group

	Group 1* n (%)	Group 2* n (%)	Group 3* n (%)	Group 4* n (%)	Total n (%)
Summary of PIL/ ICD groups	28 (32.94)	21 (24.71)	17 (20.00)	19 (22.35)	85 (100.00)
Highest level of education					
High school	11 (39.29)	11 (52.38)	7 (41.18)	7 (36.84)	36 (42.35)
Tertiary education	17 (60.71)	10 (47.62)	10 (58.82)	12 (63.16)	49 (57.65)
Race					
Black	1 (3.57)	2 (9.52)	1 (5.88)	6 (31.58)	10 (11.76)
White	27 (96.43)	19 (90.48)	16 (94.12)	13 (68.42)	75 (88.24)
Gender					
Male	14 (50.00)	11 (52.38)	16 (94.12)	15 (78.95)	56 (65.88)
Female	14 (50.00)	10 (47.62)	1 (5.88)	4 (21.05)	29 (34.12)
Question 1					
A	1 (3.57)	1 (4.76)	0 (0.00)	0 (0.00)	2 (2.35)
B (correct answer)	25 (89.29)	20 (95.24)	17 (100.00)	18 (94.74)	80 (94.12)
C	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
D	1 (3.57)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.18)
Not answered/Don't know	1 (3.57)	0 (0.00)	0 (0.00)	1 (5.26)	2 (2.35)
Question 2					
A	11 (39.29)	10 (47.62)	11 (64.71)	8 (42.11)	40 (47.06)
B	11 (39.29)	3 (14.29)	0 (0.00)	5 (26.32)	19 (22.35)
C	0 (0.00)	1 (4.76)	0 (0.00)	0 (0.00)	1 (1.18)
D (correct answer)	4 (14.29)	5 (23.81)	4 (23.53)	3 (15.79)	16 (18.82)
Not answered/Don't know	2 (7.14)	2 (9.52)	2 (11.76)	3 (15.79)	9 (10.59)
Question 3					
A (correct answer)	19 (67.86)	16 (76.19)	17 (100.00)	17 (89.47)	69 (81.18)
B	2 (7.14)	0 (0.00)	0 (0.00)	0 (0.00)	2 (2.35)
C	2 (7.14)	1 (4.76)	0 (0.00)	1 (5.26)	4 (4.71)
D	2 (7.14)	1 (4.76)	0 (0.00)	1 (5.26)	4 (4.71)
Not answered/Don't know	3 (10.71)	3 (14.29)	0 (0.00)	0 (0.00)	6 (7.06)
Question 4					
A (correct answer)	3 (10.71)	6 (28.57)	5 (29.41)	4 (21.05)	18 (21.18)
B	3 (10.71)	0 (0.00)	2 (11.76)	3 (15.79)	8 (9.41)
C	18 (64.29)	9 (42.86)	9 (52.94)	8 (42.11)	44 (51.76)
D	2 (7.14)	4 (19.05)	0 (0.00)	3 (15.79)	9 (10.59)
Not answered/Don't know	2 (7.14)	2 (9.52)	1 (5.88)	1 (5.26)	6 (7.06)
Question 5					
A	1 (3.57)	3 (14.29)	1 (5.88)	1 (5.26)	6 (7.06)
B (correct answer)	10 (35.71)	15 (71.43)	14 (82.35)	16 (84.21)	55 (64.71)
C	15 (53.57)	0 (0.00)	2 (11.76)	2 (10.53)	19 (22.35)
D	1 (3.57)	1 (4.76)	0 (0.00)	0 (0.00)	2 (2.35)
Not answered/Don't know	1 (3.57)	2 (9.52)	0 (0.00)	0 (0.0)	3 (3.53)

* Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session

Sixty one percent (61%) of volunteers in group 1, 48% of volunteers in group 2, 59% of volunteers in group 3 and 4, have had a tertiary education. In total, 58% of volunteers have had tertiary education. Thirty nine percent (39%) of subjects in group 1, 52% of subjects in

group 2, 41% of volunteers in group 3 and 37% of volunteers in group 4 had high school education. In total, 42% of the volunteers had high school education.

Ninety six percent (96%) of volunteers in group 1, 90% of volunteers in group 2, 94% in group 3 and 68% of volunteers in group 4 were white. In total, 88% of the volunteers were white. Four percent (4%) of volunteers in group 1, 10% of volunteers in group 2, 6% of volunteers in group 3 and 32% of volunteers in group 4 were black. In total, 12% of the volunteers were black.

In total, 34% of the volunteers were female of which 50% were in group 1, 48% were in group 2, 6% were in group 3 and 21% were in group 4. Sixty six percent of the total volunteers were male of which 50% were in group 1, 52% were in group 2, 94% were in group 3 and 79% were in group 4.

Table 1: Categorical Variables by Group (continued)

	Group 1* n (%)	Group 2* n (%)	Group 3* n (%)	Group 4* n (%)	Total n (%)
Summary of PIL/ ICD methods	28 (32.94)	21 (24.71)	17 (20.00)	19 (22.35)	85 (100.00)
Question 6					
A (correct answer)	26 (92.86)	20 (95.24)	17 (100.00)	19 (100.00)	82 (96.47)
B	1 (3.57)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.18)
C	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
D	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Not answered/Don't know	1 (3.57)	1 (4.76)	0 (0.00)	0 (0.00)	2 (2.35)
Question 7					
A	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
B	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
C (correct answer)	20 (71.43)	15 (71.43)	15 (88.24)	18 (94.74)	68 (80.00)
D	4 (14.29)	2 (9.52)	2 (11.76)	1 (5.26)	9 (10.59)
Not answered/Don't know	4 (14.29)	4 (19.05)	0 (0.00)	0 (0.00)	8 (9.41)
Question 8					
A	2 (7.14)	6 (58.57)	4 (23.53)	2 (10.53)	14 (16.47)
B	5 (17.86)	2 (9.52)	4 (23.53)	3 (14.79)	14 (16.47)
C	1 (3.57)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.18)
D (correct answer)	18 (64.29)	11 (52.38)	7 (41.18)	12 (63.16)	48 (56.47)
Not answered/Don't know	2 (7.14)	2 (9.52)	2 (11.76)	2 (10.53)	8 (9.41)
Question 9					
A	0 (0.00)	1 (4.76)	1 (5.88)	0 (0.00)	2 (2.35)
B	8 (28.57)	0 (0.00)	3 (17.65)	1 (5.26)	12 (14.12)
C	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
D (correct answer)	10 (35.71)	18 (85.71)	12 (70.59)	17 (89.47)	57 (67.06)
Not answered/Don't know	10 (35.71)	2 (9.52)	1 (5.88)	1 (5.26)	14 (16.47)
Question 10					
A	6 (21.43)	4 (19.05)	2 (11.76)	1 (5.26)	13 (15.29)
B	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
C (correct answer)	18 (64.29)	15 (71.43)	14 (82.35)	15 (78.95)	62 (72.94)
D	0 (0.00)	1 (4.76)	0 (0.00)	0 (0.00)	1 (1.18)
Not answered/Don't know	4 (14.29)	1 (4.76)	1 (5.88)	3 (15.79)	9 (10.59)

* Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session

Table 1: Categorical Variables by Group (continued)

	Group 1* n (%)	Group 2* n (%)	Group 3* n (%)	Group 4* n (%)	Total n (%)
Summary of PIL/ ICD methods	28 (32.94)	21 (24.71)	17 (20.00)	19 (22.35)	85 (100.00)
Question 11					
A	0 (0.00)	0 (0.00)	0 (0.00)	3 (15.79)	3 (3.53)
B (correct answer)	16 (57.14)	13 (61.90)	11 (64.71)	7 (36.84)	47 (55.29)
C	1 (3.57)	0 (0.00)	0 (0.00)	1 (5.26)	2 (2.35)
D	8 (28.57)	6 (28.57)	5 (29.41)	7 (36.84)	26 (30.59)
Not answered/Don't know	3 (10.71)	2 (9.52)	1 (5.88)	1 (5.26)	7 (8.24)
Question 12					
A	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
B	7 (25.00)	3 (14.29)	2 (11.76)	5 (26.32)	17 (20.00)
C (correct answer)	18 (64.29)	15 (71.43)	15 (88.24)	13 (68.42)	61 (71.76)
D	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Not answered/Don't know	3 (10.71)	3 (14.29)	0 (0.00)	1 (5.26)	7 (8.24)
Question 13					
A	0 (0.00)	1 (4.76)	0 (0.00)	0 (0.00)	1 (1.18)
B	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
C (correct answer)	25 (89.29)	16 (76.19)	16 (94.12)	14 (73.68)	71 (83.53)
D	2 (7.14)	2 (9.52)	1 (5.88)	2 (10.53)	7 (8.24)
Not answered/Don't know	1 (3.57)	2 (9.52)	0 (0.00)	3 (15.79)	6 (7.06)
Question 14					
A	4 (14.29)	1 (4.76)	0 (0.00)	0 (0.00)	5 (5.88)
B (correct answer)	19 (67.86)	15 (71.43)	13 (76.47)	13 (68.42)	60 (70.59)
C	5 (17.86)	2 (9.52)	3 (17.65)	5 (26.32)	15 (17.65)
D	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Not answered/Don't know	0 (0.00)	3 (14.29)	1 (5.88)	1 (5.26)	5 (5.88)
Question 15					
A (correct answer)	22 (78.57)	17 (80.95)	11 (64.71)	17 (89.47)	67 (78.82)
B	1 (3.57)	1 (4.76)	1 (5.88)	0 (0.00)	3 (3.53)
C	1 (3.57)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.18)
D	4 (14.29)	1 (4.76)	4 (23.53)	1 (5.26)	10 (11.76)
Not answered/Don't know	0 (0.00)	2 (9.52)	1 (5.88)	1 (5.26)	4 (4.71)

* Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session

Table 1: Categorical Variables by Group (continued)

	Group 1* n (%)	Group 2* n (%)	Group 3* n (%)	Group 4* n (%)	Total n (%)
Summary of PIL/ ICD methods	28 (32.94)	21 (24.71)	17 (20.00)	19 (22.35)	85 (100.00)
Question 16					
A	2 (7.14)	0 (0.00)	1 (5.88)	2 (10.53)	5 (5.88)
B	1 (3.57)	3 (14.29)	0 (0.00)	1 (5.26)	5 (5.88)
C (correct answer)	22 (78.57)	13 (61.90)	16 (94.12)	15 (78.95)	66 (77.65)
D	1 (3.57)	1 (4.76)	0 (0.00)	0 (0.00)	2 (2.35)
Not answered/Don't know	2 (7.14)	4 (19.05)	0 (0.00)	1 (5.26)	7 (8.24)
Question 17					
A	12 (42.86)	8 (38.10)	9 (52.94)	6 (31.58)	35 (41.18)
B (correct answer)	6 (21.43)	5 (23.81)	6 (35.29)	10 (52.63)	27 (31.76)
C	1 (3.57)	1 (4.76)	1 (5.88)	0 (0.00)	3 (3.53)
D	8 (28.57)	4 (19.05)	1 (5.88)	1 (5.26)	14 (16.47)
Not answered/Don't know	1 (3.57)	3 (14.29)	0 (0.00)	2 (10.53)	6 (7.06)
Question 18					
A	0 (0.00)	1 (4.76)	2 (11.76)	0 (0.00)	3 (3.53)
B (correct answer)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
C	4 (14.29)	1 (4.76)	0 (0.00)	2 (10.53)	7 (8.24)
D	23 (82.14)	15 (71.43)	15 (88.24)	15 (78.95)	68 (80.00)
Not answered/Don't know	1 (3.57)	4 (19.05)	0 (0.00)	2 (10.53)	7 (8.24)
Question 19					
A	6 (21.43)	3 (14.29)	2 (11.76)	5 (26.32)	16 (18.82)
B (correct answer)	20 (71.43)	14 (66.67)	15 (88.24)	13 (68.42)	62 (72.64)
C	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
D	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Not answered/Don't know	2 (7.14)	4 (19.05)	0 (0.00)	1 (5.26)	7 (8.24)
Question 20					
A	6 (21.43)	2 (9.52)	3 (17.65)	3 (15.79)	14 (16.47)
B	6 (21.43)	12 (57.14)	2 (11.76)	4 (21.05)	24 (28.24)
C (correct answer)	13 (46.43)	3 (14.29)	9 (52.94)	10 (52.63)	35 (41.18)
D	3 (10.71)	1 (4.76)	2 (11.76)	1 (5.26)	7 (8.24)
Not answered/Don't know	0 (0.00)	3 (14.29)	1 (5.88)	1 (5.26)	5 (5.88)

* Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session

Table 1: Categorical Variables by Group (continued)

	Group 1* n (%)	Group 2* n (%)	Group 3* n (%)	Group 4* n (%)	Total n (%)
Summary of PIL/ ICD methods	28 (32.94)	21 (24.71)	17 (20.00)	19 (22.35)	85 (100.00)
Question 21					
A	0 (0.00)	1 (4.76)	0 (0.00)	1 (5.26)	2 (2.35)
B	0 (0.00)	3 (14.29)	1 (5.88)	1 (5.26)	5 (5.88)
C	9 (32.14)	1 (4.76)	4 (23.53)	3 (15.79)	17 (20.00)
D (correct answer)	17 (60.71)	14 (66.67)	12 (70.59)	11 (57.89)	54 (63.53)
Not answered/Don't know	2 (7.14)	2 (9.52)	0 (0.00)	3 (15.79)	7 (8.24)
Question 22					
A (correct answer)	26 (92.86)	16 (76.19)	16 (94.12)	15 (78.95)	73 (85.88)
B	1 (3.57)	0 (0.00)	1 (5.88)	0 (0.00)	2 (2.35)
C	1 (3.57)	1 (4.76)	0 (0.00)	2 (10.53)	4 (4.71)
D	0 (0.00)	2 (9.52)	0 (0.00)	1 (5.26)	3 (3.53)
Not answered/Don't know	0 (0.00)	2 (9.52)	0 (0.00)	1 (5.26)	3 (3.53)
Question 23					
A	2 (7.14)	2 (9.52)	0 (0.00)	2 (10.53)	6 (7.06)
B	4 (14.29)	2 (9.52)	1 (5.88)	1 (5.26)	8 (9.41)
C	2 (7.14)	0 (0.00)	0 (0.00)	0 (0.00)	2 (2.35)
D (correct answer)	19 (67.86)	14 (66.67)	16 (94.12)	15 (78.95)	64 (75.29)
Not answered/Don't know	1 (3.57)	3 (14.29)	0 (0.00)	1 (5.26)	5 (5.88)
Question 24					
A (correct answer)	27 (96.43)	16 (76.19)	17 (100.00)	13 (68.42)	73 (85.88)
B	1 (3.57)	3 (14.29)	0 (0.00)	5 (26.32)	9 (10.59)
C	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
D	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Not answered/Don't know	0 (0.00)	2 (9.52)	0 (0.00)	1 (5.26)	3 (3.53)
Question 25					
A (correct answer)	27 (96.43)	19 (90.48)	16 (94.12)	17 (89.47)	79 (92.94)
B	0 (0.00)	0 (0.00)	1 (5.88)	0 (0.00)	1 (1.18)
C	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
D	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Not answered/Don't know	1 (3.57)	2 (9.52)	0 (0.00)	2 (10.53)	5 (5.88)

* Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session

3.1.1.2 Continuous Variables

Table 2: Continuous Variables by Group

	Group 1*	Group 2*	Group 3*	Group 4*	Total
Age (years)					
n	28	19	16	18	81
Mean	26.97	27.37	24.71	25.11	26.20
Median	21.45	23.05	22.35	24.45	22.21
SD	10.90	10.68	7.31	4.81	9.05
Minimum	18.29	19.50	18.70	18.00	18.00
Maximum	52.14	56.60	42.96	33.74	56.60
IQR	20.08;33.25	20.57;34.58	20.16;23.25	21.27;28.26	20.49;28.01

* Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session

Note: the ages of four volunteers were unknown

The average age of all volunteers was 26 years. The youngest volunteer was 18 years old and the oldest volunteer was 57 years old.

The average age for the volunteers in group 1 was 27 years of which the youngest volunteer was 18 years and the oldest volunteer was 52 years old.

The youngest volunteer in group 2 was 20 years old and the oldest volunteer was 57 years old. Thus, the average age for volunteers in group 2 was 27 years old.

Similarly, the youngest volunteer in group 3 was 19 years old and the oldest volunteer was 43 years old. The average age of the volunteers in group 3 was 25 years old.

Lastly, the youngest volunteer in group 4 was 18 years old and the oldest volunteer in group 4 was 34 years old. The average age of volunteers in group 4 was 26 years old.

3.1.1.3 Number of questions answered correctly

Table 3: Number of questions answered correctly by Group

	Group 1* n	Group 2* n	Group 3* n	Group 4* n	Total n
Summary of PIL/ ICD methods	28	21	17	19	85
Nr of questions answered correctly					
One (1)	0	1	0	0	1
Six (6)	0	1	0	0	1
Seven (7)	1	0	0	0	1
Nine (9)	0	0	0	1	1
Ten (10)	2	0	0	0	2
Eleven (11)	1	0	0	1	2
Twelve (12)	2	1	0	1	4
Thirteen (13)	1	0	0	0	1
Fourteen (14)	4	4	0	0	8
Fifteen (15)	1	0	0	1	2
Sixteen (16)	3	1	1	2	7
Seventeen (17)	4	2	5	4	15
Eighteen (18)	5	7	4	2	18
Nineteen (19)	2	1	4	4	11
Twenty (20)	2	2	1	1	6
Twenty one (21)	0	1	2	1	4
Twenty two (22)	0	0	0	1	1

* Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session

Out of a total of 25 questions, the minimum number of questions answered correctly was one (recorded by one volunteer) and the maximum 22 (recorded by one volunteer). The mode (i.e. most common number of questions answered correctly) was 18 correct answers, recorded by 18 volunteers.

The highest score (22 correct answers out of a potential of 25) was recorded in group 4 (Read PIL/ ICD, presentation and Q&A session) and the lowest score (1 correct answer) was recorded by a volunteer who participated in group 2.

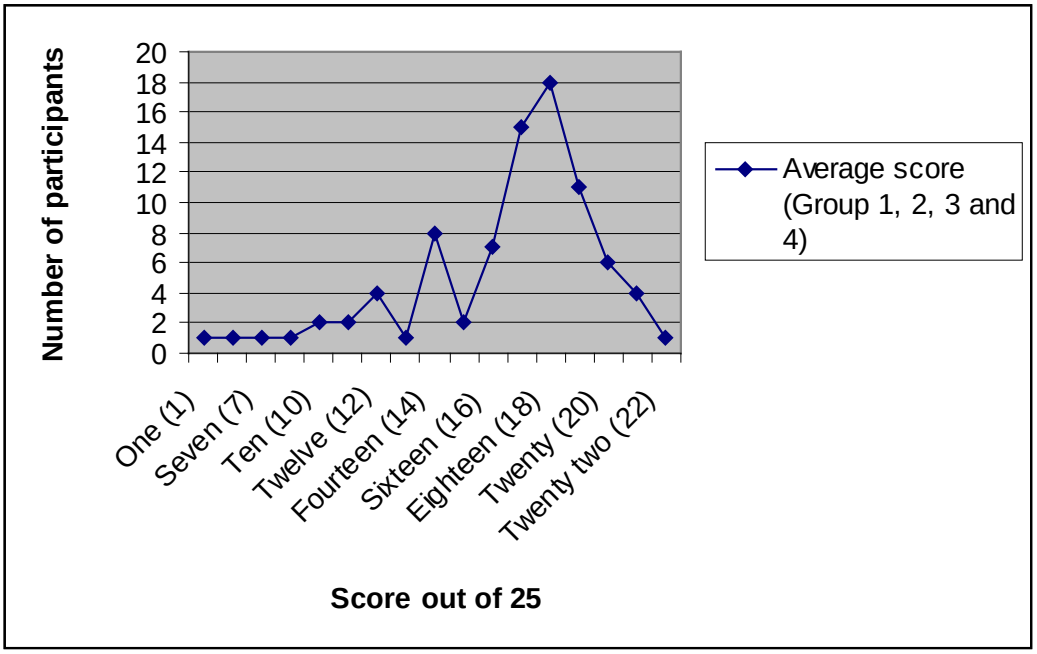
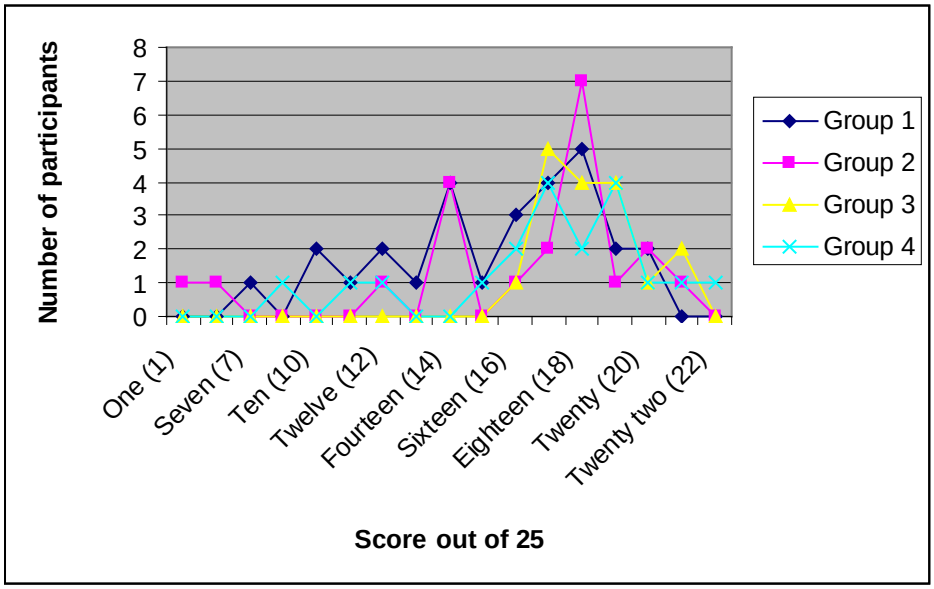


Figure 7: Frequency distribution of number of correct answers (n=85)

The minimum number of questions answered correctly (out of a total of 25 questions) by volunteers in group 1 was seven (recorded by one volunteer) and the maximum 20 (recorded by two volunteers). The mode (i.e. most common number of questions answered correctly) was 18 correct answers, recorded by 5 volunteers.



* Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session

Figure 8: Frequency distribution of number of correct answers by Group

Out of a total of 25 questions, the minimum number of questions answered correctly by volunteers in group 2 was one (recorded by one volunteer) and the maximum 21 (recorded by one volunteer). The mode (i.e. most common number of questions answered correctly) was 18 correct answers, recorded by 7 volunteers.

The minimum number of questions answered correctly (out of a total of 25 questions) by volunteers in group 3 was sixteen (recorded by one volunteer) and the maximum 22 (recorded by two volunteers). The mode (i.e. most common number of questions answered correctly) was 17 correct answers, recorded by 5 volunteers.

Out of a total of 25 questions, the minimum number of questions answered correctly by volunteers in group 4 was nine (recorded by one volunteer) and the maximum 22 (recorded by one volunteer). The mode (i.e. most common number of questions answered correctly) was 17 and 19 correct answers, recorded by 4 volunteers each.

3.1.2 Objective 2: Identifying the most effective PIL/ ICD method

Table 4: Calculated mark (number of questions answered correctly)

	Group 1*	Group 2*	Group 3*	Group 4*	Total
n	28	21	17	19	85
Mean	15.36	15.76	18.29	16.94	16.40
Median	16.00	18.00	18.00	17.00	17.00
SD	3.32	4.75	1.45	3.32	3.60
Minimum	7.00	1.00	16.00	9.00	1.00
Maximum	20.00	21.00	21.00	22.00	22.00

* Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session

In Table 4, the “calculated mark” refers to the number of questions answered correctly out of a possible 25 questions.

Table 5: Calculated mark % ((calculated mark/25)*100)

	Group 1*	Group 2*	Group 3*	Group 4*	Total
n	28	21	17	19	85
Mean	61.43	63.05	73.18	67.79	65.60
Median	64.00	72.00	72.00	68.00	68.00
SD	13.30	19.01	5.79	13.30	14.40
Minimum	28.00	4.00	64.00	36.00	4.00
Maximum	80.00	84.00	84.00	88.00	88.00

* Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session

In Table 5, the "calculated mark %" = (calculated mark/25)*100.

Based on the averages (means) of the "calculated mark" and "calculated mark %", group 3 scored the highest (68%), therefore, reading the PIL/ICD and attending a presentation, was the most effective way to transfer information regarding the PIL/ICD.

CHAPTER 4: DATA ANALYSIS AND DISCUSSION

4.1 Data Analysis and Discussion

The five questions that scored the highest average score in ascending order (i.e. that were answered correctly by the most volunteers) were:

- Question 6: "You will be compensated for you participation in the following way" (correct response was the compensation for the study)
- Question 1: "Participation in this trial is…" (correct response was "voluntary")
- Question 25: "The protocol for this study has been approved by an Ethics Committee" (correct response was "true")
- Question 22: "Should you experience any adverse effects due to your participation in this study, you will…" (correct response was "receive medical care free of charge until you are healthy again")
- Question 24: "The right to compensation is legally guaranteed" (correct response was "true")

Likewise, the questions that scored the lowest average score in ascending order (i.e. the questions that were answered incorrectly by the most volunteers) were:

- Question 18: "After the clinical trial, your biological samples will be stored for…" (correct response was "15 years")
- Question 2: "If you withdraw from the clinical trial you will lose the following benefits you would otherwise be entitled to…" (correct response was "none")
- Question 4: "The following staff will know which volunteers has received xxx or xxx" (the correct response depended on the trial design i.e. double blind)
- Question 17: "Any records/data collected from you during the course of this study will…" (correct response was "will not be used for any other purpose other than this study")
- Question 20: "The doctor involved in this study will be acting as…" (correct response was "the investigator and your physician")

Table 6: Ranking of questions in order of number of correct answers (total)

Rank	*Question #*	*Group 1*	*Group 2*	*Group 3*	*Group 4*	*Combined Total*
1	Question 6	92.86	95.24	100	100	96.47
2	Question 1	89.29	95.24	100	94.74	94.12
3	Question 25	96.43	90.48	94.12	89.47	92.94
4	Question 22	92.86	76.19	94.12	78.95	85.88
5	Question 24	96.43	76.19	100	68.42	85.88
6	Question 13	89.29	76.19	94.12	73.68	83.53
7	Question 3	67.86	76.19	100	89.47	81.18
8	Question 7	71.43	71.43	88.24	94.74	80
9	Question 15	78.57	80.95	64.71	89.47	78.82
10	Question 16	78.57	61.9	94.12	78.95	77.65
11	Question 23	67.86	66.67	94.12	78.95	75.29
12	Question 10	64.29	71.43	82.35	78.95	72.94
13	Question 19	71.43	66.67	88.24	68.42	72.64
14	Question 12	64.29	71.43	88.24	68.42	71.76
15	Question 14	67.86	71.43	76.47	68.42	70.59
16	Question 9	35.71	85.71	70.59	89.47	67.06
17	Question 5	35.71	71.43	82.35	84.21	64.71
18	Question 21	60.71	66.67	70.59	57.89	63.53
19	Question 8	64.29	52.38	41.18	63.16	56.47
20	Question 11	57.14	61.9	64.71	36.84	55.29
21	Question 20	46.43	14.29	52.94	52.63	41.18
22	Question 17	21.43	23.81	35.29	52.65	31.76
23	Question 4	10.71	28.57	29.41	21.05	21.18
24	Question 2	14.29	23.81	23.53	15.79	18.82
25	Question 18	0	0	0	0	0

4.1.1 Comprehension of clinical trial concepts

The most insightful study regarding volunteer comprehension was conducted recently in Mali, West Africa[8] whereby a questionnaire containing nine questions was administered to assess volunteer comprehension regarding the following topics:

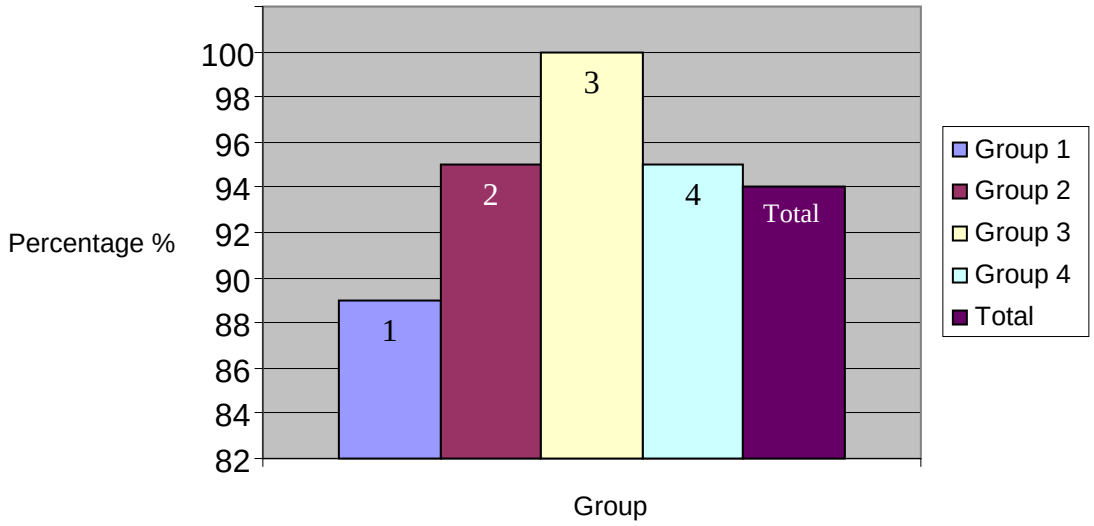
- Voluntary participation
- Compensation
- Withdrawal criteria
- Withdrawal consequence
- Study versus treatment

- Study administration
- Randomization and placebo
- Side effects
- Lay scientific knowledge

No other relevant data is available. The results of this project will be assessed according to the same concepts.

4.1.1.1 Voluntary participation

In total, 94% of the volunteers understood that their participation was voluntary (Question 1).

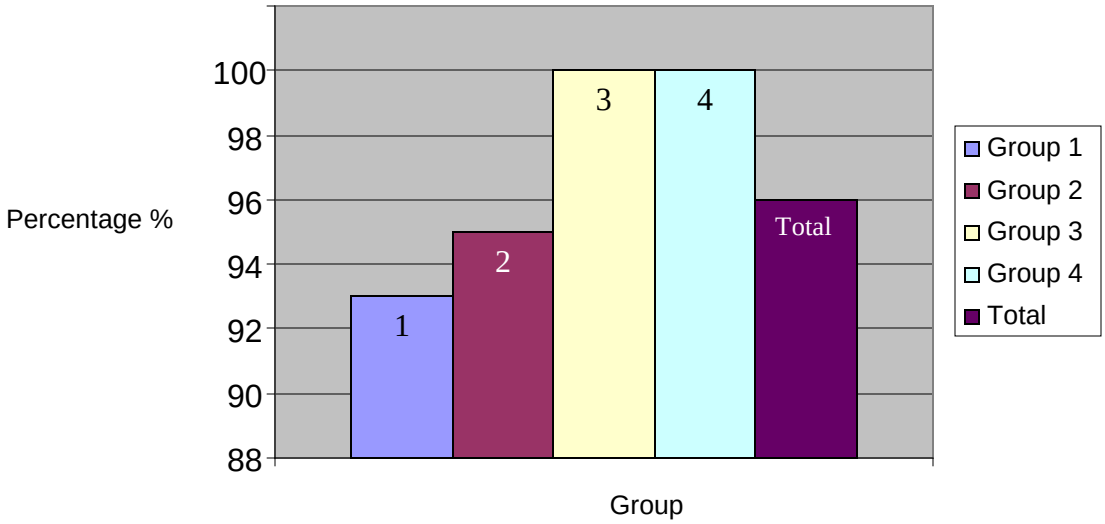


Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session
percentage % = [number of correct answers/ group (n)] * 100

Figure 9: Voluntary participation (Question 1)

4.1.1.2 Compensation

The concept of compensation is well understood as 96% of the volunteers answered this question correctly (Question 6). All the volunteers who participated in the groups utilizing visual aid (Group 3 and 4) answered the question regarding compensation consistently correct.

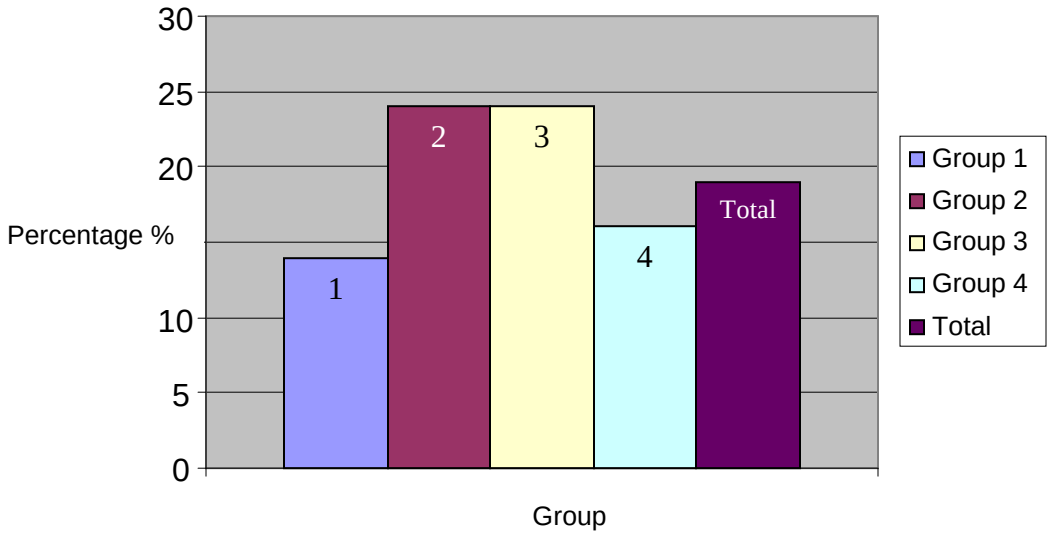


Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session
percentage % = [number of correct answers/ group (n)] * 100

Figure 10: Compensation (Question 6)

4.1.1.3 Withdrawal Consequence

In total, only 19% of the volunteers answered the question regarding withdrawal consequence (Question 2) correctly with no clear advantage in a particular group.

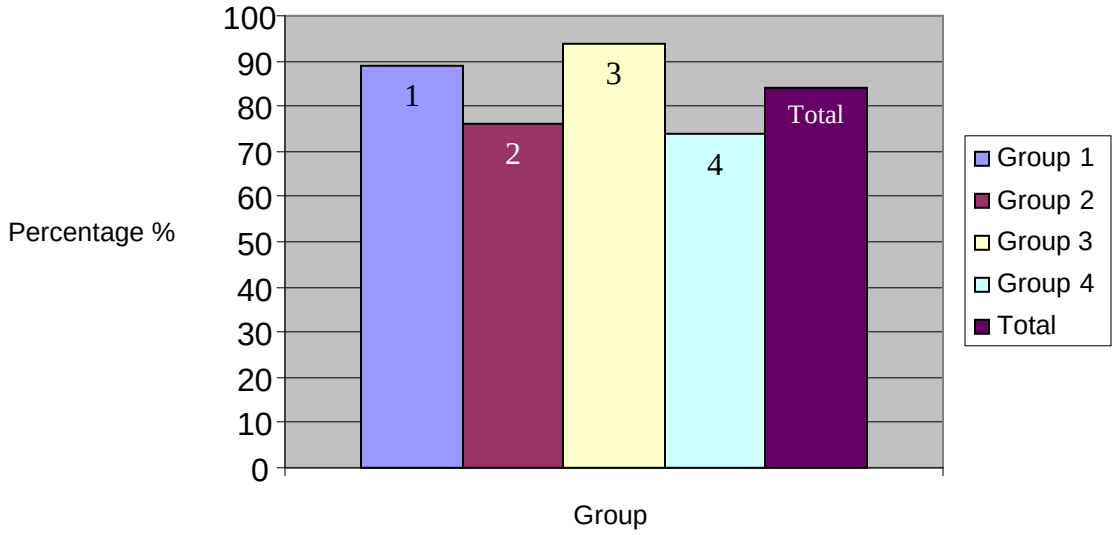


* Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session, percentage % = [number of correct answers/ group (n)] * 100

Figure 11: Withdrawal Consequence (Question 2)

4.1.1.4 Study *versus* treatment

Eighty four percent (84%) of volunteers answered the question regarding the study versus alternative treatment (Question 13) correctly, also with no clear advantage in a particular group.



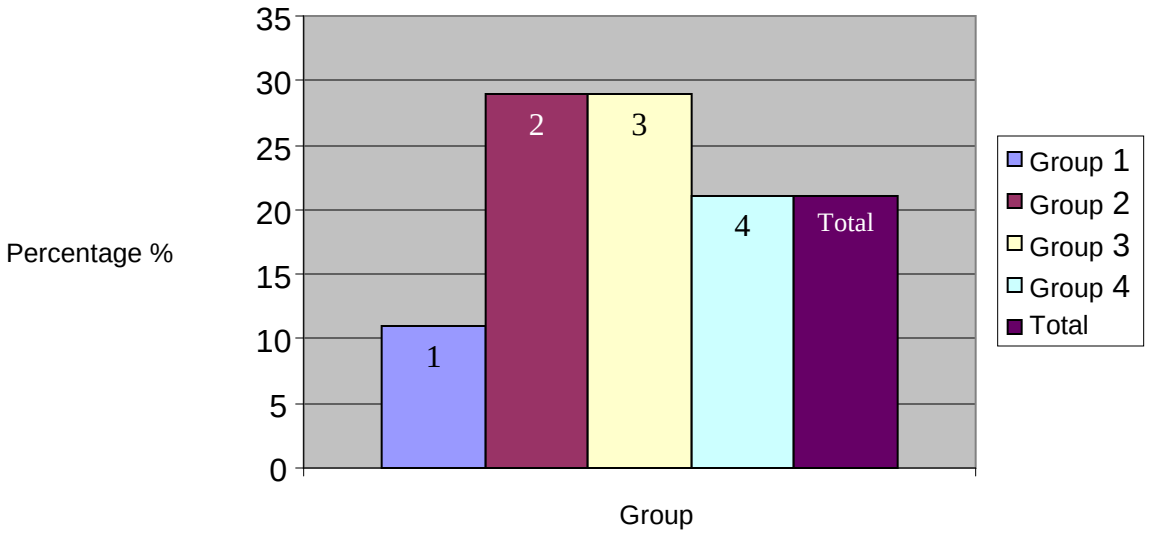
* Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session
percentage % = [number of correct answers/ group (n)] * 100

Figure 12: Study versus treatment (Question 13)

4.1.1.5 Study Methodology

The concepts of study administration was tested by asking questions regarding the volunteer's duration of participation (Question 5), the identity of the sponsor (Question 16) and the duration of archiving (Question 18). Only 36% of the volunteers who had only read the PIL/ ICD could answer Question 5 correctly compared to 71% in group 2, 82% in group 3 and 84% of volunteers in group 4. Seventy seven percent (77%) of the volunteers could correctly identify the sponsor (Question 16) whereas 0% of the volunteers knew how long blood samples will be stored for (Question 18).

Concepts regarding research/study methodology (Question 4) (e.g. double/single blinding) was not well understood as only 21% of the volunteers answered this question correctly.

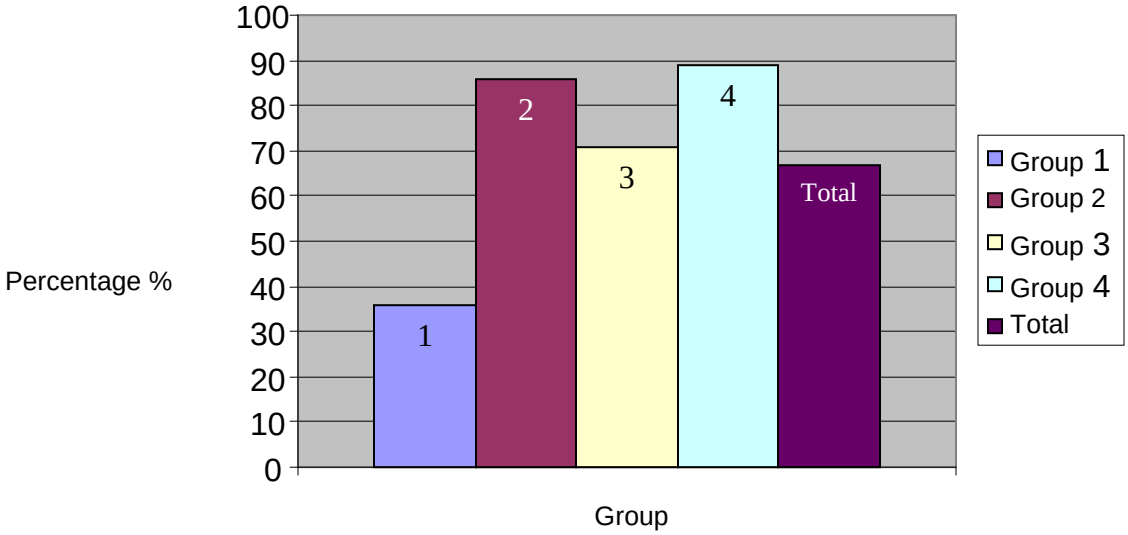


* Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session
percentage % = [number of correct answers/ group (n)] * 100

Figure 13: Study methodology (Question 4)

4.1.1.6 Side effects

After only reading the PIL/ ICD (Group 1), 64% of volunteers answered the question regarding side effects (Question 9) incorrectly and 37% of all volunteers answered the question regarding side effects (Question 9) incorrectly.

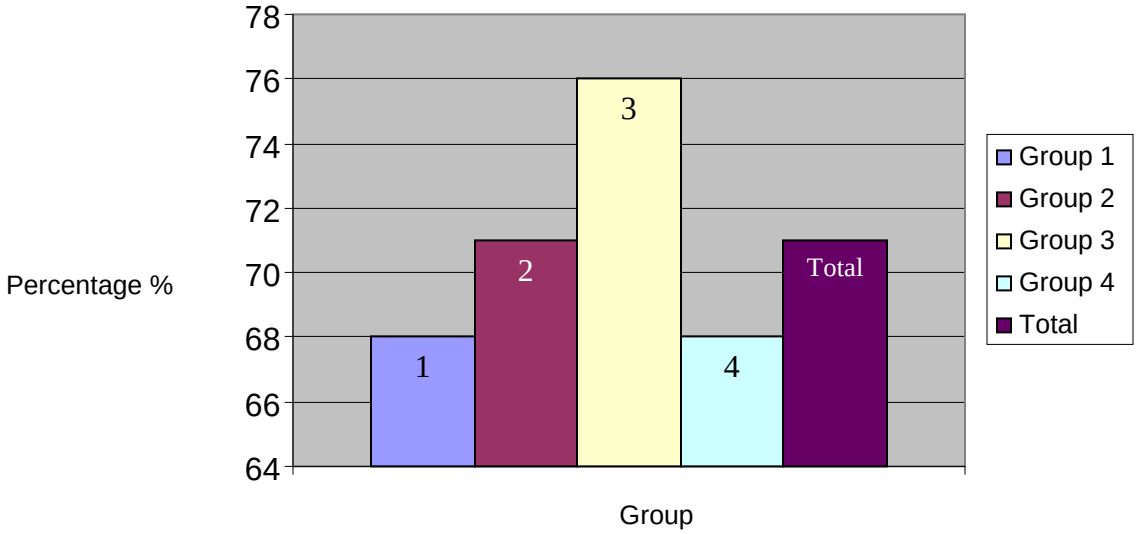


* Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session, percentage % = [number of correct answers/ group (n)] * 100

Figure 14: Side effects (Question 9)

4.1.1.7 Volunteer protection

In total, 71% of volunteers understood how their data will be protected (Question 14).



* Group 1 = Read PIL/ ICD only, Group 2 = Read PIL/ ICD and Q&A session, Group 3 = Read PIL/ ICD and presentation, Group 4 = Read PIL/ ICD, presentation and Q&A session
percentage % = [number of correct answers/ group (n)] * 100

Figure 15: Volunteer protection (Question 14)

4.1.2 Method of Data Transfer

Although Group 3 (reading the PIL/ ICD and attending the presentation) showed a clear advantage, one should also consider that Group 4 (Reading the PIL/ ICD, attending the presentation and the question and answer session) delivered the second highest results.

Therefore, the volunteers who attended the methods of data transfer which included a visual component (i.e. a presentation), scored on average higher than their counterparts who participated in Group 1 and Group 2 (i.e. methods that did not include a visual stimulus).

It seems that the TGN 1412 trial was not conducted in vain. It prompted a number of new measures, suggestions and investigations from a variety of academic and regulatory sources in order to improve the safety of first-in-man studies.

At the time of writing this research report, the European Medicines Agency (EMEA) have released a guideline aimed specifically at improving the safety of Phase I trials. It is intended to help companies move potentially high risk medicines into early clinical studies. It covers quality aspects, non-clinical testing strategies and designs for first-in-man clinical trials, including the first dose, dose escalation, intervals between doses in healthy volunteers and risk management[12,16].

Although volunteer protection is a topic which has been debated, one can not ignore the benefit volunteers derive from their participation in clinical trials. It has been well observed that volunteers receiving placebo are generally doing better than their counterparts who are not participating in clinical trials. This may be contributed to the fact that they visit their clinicians more often, clinicians are more accessible and better compliance with their medication because they are aware that this is being checked. Therefore, the benefit to risk ratio should be thoroughly evaluated.

In conclusion, there seems to be no clear answer as to how valid the Informed Consent process really is, but from these results one can conclude that by including a visual component to the informed consent process, the level of volunteer comprehension is increased (Group 3 and 4).

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

5.1 Limitations

True-false and multiple choice questions do represent a degree of limitation as volunteers can get a percentage of the questions correct by guessing. Volunteers can get 50% of true-false questions correct by guessing and 25% of multiple choice questions containing 4 possible answers[13].

Nonetheless, comprehension scores may still be higher on multiple choice questionnaires in comparison to when researchers ask the volunteers to tell them what they remembered about the trial.

The sample size (20 questionnaires on each communication strategy, 80 questionnaires in total) was based upon the number of questionnaires that could realistically be collected rather than a formal statistical calculation. FARMOVS/PAREXEL conducts mainly Phase I and bioanalytical studies, therefore, the number of volunteers being screened was relatively small. Only descriptive statistics could be performed rather than a formal statistical comparison.

To collect 80 questionnaires within the proposed timelines proved to be more challenging than originally anticipated as the Medicines Control Council (MCC) approval of trials was severely delayed. This resulted in trials either being cancelled or delayed. There were long periods of time when no screening for any trials could be conducted.

A further limitation is that participants from the various indications (HIV, Asthma, Seizures and Alcohol Addiction) could not be distributed equally amongst the four investigational groups. This could however not be conducted differently as the project was approved by the facility's management on condition that it did not add additional time to the normal functioning of the facility. Further investigation is required to determine whether the indication of the clinical trial has an effect on the level of comprehension.

As the demographical (age, race and gender) composition of each group was unbalanced (due to the fact that screening volunteers were used), no conclusions can be made with respect to the demographical influence on the group scores.

Although the average scores where higher in the groups that attended the presentations (Group 3 and 4), one must keep in mind that all four groups of volunteers had either high school or tertiary education (see table 1). The volunteers are thus familiar with presentations and may in turn, increase the level of comprehension.

Therefore, it would be difficult to predict the general South-African population's comprehension (and retention) of information shared *via* a presentation.

Further investigation is thus needed into the development of valid informed consents in South-Africa since this project only included volunteers with an acceptable level of education, income and age and can therefore not be classified as "vulnerable".

5.2 Conclusions and Recommendation

During this project, it was noted that volunteers understood clinical trial concepts better when visual aids were used during the informed consent process (Group 3 and Group 4):

- Read PIL/ ICD only (Group 1): Mean calculated mark of 61.43%
- Read PIL/ ICD and Q&A session (Group 2): Mean calculated mark of 63.05%
- Read PIL/ ICD and presentation (Group 3): Mean calculated mark of 73.18%
- Read PIL/ ICD, presentation and Q&A session (Group 4): Mean calculated mark of 67.79%

From the above results one can conclude that volunteers who attended the methods of data transfer which included a visual component (i.e. a presentation) (Group 3 and 4), scored on average higher than their counterparts who participated in methods that did not include a visual stimulus (Group 1 and Group 2).

It is expected that a higher number of questionnaires would have demonstrated a more significant difference between the non-visual methods of data transfer (Group 1 and 2) and the visual methods (Group 3 and 4).

Concepts that are not well understood within the South-African context are:

- withdrawal consequence (Question 2),
- methodology such as double-blind or single blind (Question 4),
- duration of archiving (Question 18),
- protection of records/ data (Question 17), and
- the role of the investigator (Question 20)

Following this project, the following recommendations can be made in order to improve volunteer comprehension of the concepts being shared with them during the informed consent process:

- Repeat information as much as possible in as many different ways as possible
- Depending on the demographic characteristics of the group visual aids generally increases comprehension and retention of information as it captivates the audience for longer periods of time and increases comprehension.
- Keep the PIL/ICD as short as possible
- More attention should be paid to ensure volunteer's comprehension of withdrawal consequence as this was a concept that was not well understood
- More attention should be paid to concepts regarding research methodology such as double-blind/single-blind etc. as this was a concept not well understood
- Other concepts that are also not well understood include treatment alternatives, side-effects, duration of sample storage and the role of the investigator and should therefore receive more attention to improve volunteer comprehension
- Do not assume that volunteers will have a good understanding of the clinical trial after only reading the PIL/ICD as volunteers who only read the PIL/ICD had a poor understanding of concepts such as the potential side effects relative to the other methods of data transfer.

However, as the calculated mark (%) in this project are lower than expected, it is imperative that further investigation should be conducted (especially in vulnerable populations).

Despite increasing regulatory and ethical scrutiny, deficiencies still exist in volunteer comprehension of the research in which they participate, as well as differences in how comprehension is measured and assessed.

Essentially, all methods are flawed since none of the groups scored 100%. Thus, every attempt should be made to improve the current process of informed consent.

References

1. Moberly T. *Will drug trials ever be the same again?* The Pharmaceutical Journal. 2006; 276:342
2. Spilker B. *Guide to Clinical Trials.* Raven Press; 1991
3. Center Watch: special article reprint. 2002 May; 9: Issue 5:1-6
4. Williams CJ, Zwitter M. *Informed Consent in European multicentre randomized clinical trials- are volunteers really informed.* European Journal of Cancer 1994; 30(A):907-10
5. Chenaud C, Merlani P, Ricou B. *Informed Consent for research in ICU obtained before ICU admission.* Intensive care Medicine. 2006;32:439-444
6. White CS, Mason AC, Freehan M, Templeton P.A. *Informed Consent for Percutaneous lung biopsy: comparison of two consent protocols based on volunteer recall after the procedure.* American Journal of Respiratory Medicine 1995;165:1139-42
7. Molyneux CS, Peshu N, Marsh K. *Understanding of Informed Consent in a low income setting: three case studies from the Kenyan coast.* Social Science and Medicine 2004;59:2547-59
8. Krosin MT, Klitzman R, Levin B, Cheng J, Ranney M. *Problems in comprehension of informed consent in rural and peri-urban Mali, West Africa.* J Clinical Trials. 2006; 3:306-313
9. Riecken HW, Ravich R. *Informed Consent to biomedical research in Veterans Administration Hospitals.* Journal of the American Medicine Association. 1982;248:344-348
10. Bhutta ZA, Beyond Informed Consent. *Bulletin of the World Health Organization.* 2004;82:771-777
11. Council for International Organizations of Medical Sciences (CIOMS). *International Ethical Guidelines for Biomedical Research Involving Human Volunteers* [homepage on the internet]. c2002 [updated 2002 Nov; cited 2002 Nov]. Available from http://www.cioms.ch/frame_guidelines_nov_2002.htm
12. Schofield I. *Guideline puts safety first.* Good Clinical Practice Journal 2007;29

13. Hochhauser M. *Informed Consent: Reading and Understanding Are Not the Same.* Applied Clinical Trials. C2004 [updated 2004 Apr 1; cited 2007 May 11]
14. Available from: http://www.actmagazine.com/appliedclinicaltrials/content/printContentPopup.jsp?id=90594
15. Jamison H, Sher PP, Appleyard R, Levernois Y. *The use of multimedia in the Informed Consent Process.* Journal of the American Information Association, 1998;5(3):245-256
16. Verastegui LE. *Consenting of the vulnerable: the informed consent procedure in advanced cancer volunteers in Mexico.* BMC Medical Ethics. 2006;7-13
17. Baguley J. *EMEA releases draft guideline on first-in-man clinical trials.* CRA advisor. 2007;191:2-3
18. Gelsinger vs University of Pennsylvania (2002) 20 CLR5. http://sskrplaw.com/links/healthcare2.html [cited August 7, 2007]
19. Schmit J. *More drugs get slapped with lawsuits.* USA Today. 2006 [updated 2006 Aug 23; cited 2007 Sep 28] Available from: http://www.usatoday.com/money/industries/health/drugs/2006-08-23-drug-lawsuits-usat_x.htm

APPENDIX I: Obtaining informed Consent: Essential Information

Text of Guideline 5 of the International Ethical Guidelines for Biomedical Research involving human volunteers **(International Conference of Harmonization (ICH).**

Before requesting a volunteer's consent to participate in research, the investigator must provide the following information, in language or another form of communication that the volunteer can understand:

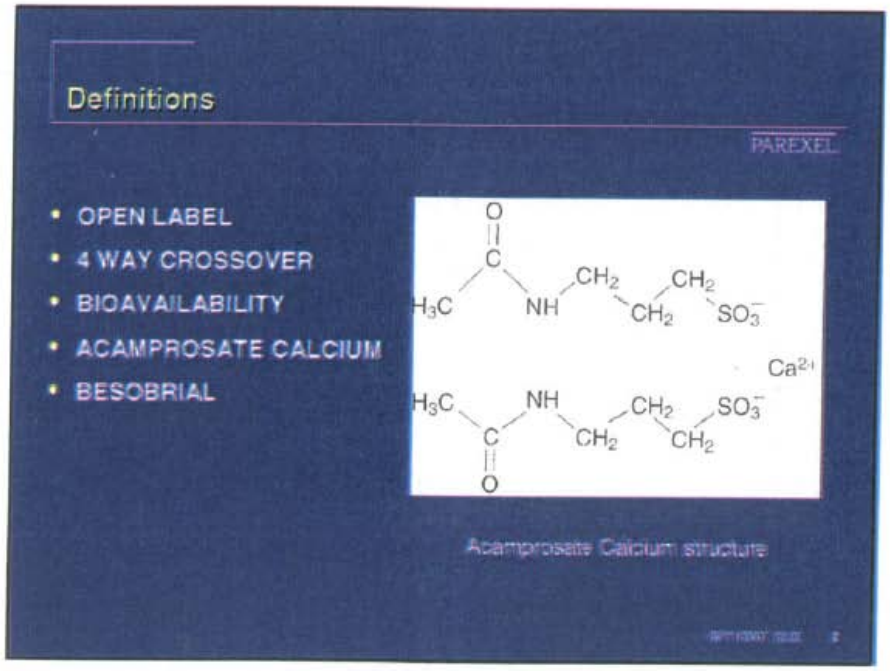
1. that the volunteer is invited to participate in research, the reasons for considering the volunteer suitable for research and the participation is voluntary;
2. that the volunteer is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she will otherwise be entitled;
3. the purpose of the research, the procedures to be carried out by the investigator and the volunteer, and an explanation of how the research differs from routine medical care;
4. for controlled trials, an explanation of the features of the research design (e.g. randomization, double blinding), and that the volunteer will not be told of the assigned treatment until the trial has been completed and the blind has been broken;
5. the expected duration of the volunteer's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the volunteer's participation in it;
6. whether money or other forms of material goods will be provided in return for the volunteer's participation and, if so, the kind and amount;
7. that, after the completion of the study, volunteers will be informed of the findings of the research in general, and volunteer volunteers will be informed of any finding that relates to their particular health status;
8. that volunteers have the right of access to their data on demand, even if these data lack immediate clinical utility (unless the ethical review committee has approved temporary or permanent non-disclosure of data, in which case the volunteers should be informed of, and given, the reasons for such non-disclosure);

9. any foreseeable risks, pain or discomfort, or inconvenience to the volunteer (or others) associated with participation in the research, including risks to the health or well-being of a volunteer's spouse or partner;
10. the direct benefits, if any, expected to result to volunteers from participating in the research;
11. the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge;
12. whether, when and how any products or interventions proven by the research to be safe and effective will be made available to volunteers after they have completed their participation in the research, and whether they will be expected to pay for them;
13. any currently available alternative interventions or courses of treatment;
14. the provisions that will be made to ensure respect for the privacy of volunteers and for the confidentiality of records in which volunteers are identified;
15. the limits, legal or other, to the investigators' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality;
16. policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a volunteer's genetic tests to immediate family relatives or to others (e.g., insurance companies or employers) without the consent of the volunteer;
17. the sponsors of the research, the institutional affiliation of the investigators, and the nature and sources of funding for the research;
18. the possible research uses, direct or secondary, of the volunteer's medical records and of biological specimens taken in the course of clinical care (see also Guidelines 4 and 18 Commentaries);
19. whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, and that volunteers have the right to decide about such future use, to refuse storage, and to have the material destroyed (see Guideline 4 Commentary);

20. whether commercial products may be developed from biological specimens, and whether the volunteer will receive monetary or other benefits from the development of such products;
21. whether the investigator is serving only as an investigator or as both investigator and the volunteer's physician;
22. the extent of the investigator's responsibility to provide medical services to the volunteer;
23. that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research, the nature and duration of such care, the name of the organization or volunteer that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment.
24. in what way, and by what organization, the volunteer or the volunteer's family or dependants will be compensated for disability or death resulting from such injury (or, when indicated, that there are no plans to provide such compensation);
25. whether or nor, in the country in which the prospective volunteer is invited to participate in research, the right to compensation is legally guaranteed;
26. That an ethical review committee has approved or cleared the research protocol.

APPENDIX II: Presentation





Tests to determine eligibility

PAREXEL

- Height and weight measurements
- Urine test
- Urine screen for drugs of abuse
- Alcohol breath test
- Blood pressure, pulse rate and body temperature observations
- Electrocardiogram (ECG)
- Chest X-ray
- Laboratory investigations: Full blood count, clinical chemistry profile and HIV and hepatitis B and C tests.
- A full medical history and information on alcohol and tobacco consumption

DRUGS OF ABUSE TESTS (to determine eligibility)

PAREXEL

- Exclusion due to positive test
- Positive tests may be repeated at the discression of the doctor

HIV AND HEPATITIS B AND C INFORMATION

PAREXEL

- Disease might cause symptoms and signs that could be mistaken for adverse events due to the study medication - study results worthless
- Study medication could dangerously aggravate conditions, such as HIV or Hepatitis
- Advantages in knowing HIV & Hepatitis status
- In case of a positive test, you will be informed by the study doctor or appropriately qualified designee
- Results are strictly confidential

CONFIDENTIAL

Note: Feel free to discuss any questions with the study doctor

Introduction

PAREXEL

Sponsor: Somaxon Pharmaceuticals, Inc.

Participation: Voluntary

Withdrawal:

- Any time upon your request
- Upon recommendation of the doctor
- If you do not comply to the protocol
- You need to undergo laboratory investigations



Purpose of the study

PAREXEL

- Compare blood levels and safety of 4 preparations of medicine
- 1 preparation already in use for alcohol abstinence (reference product)
- 3 new preparations (test product)
- ALL preparations contain the same active ingredient
- PURPOSE: To compare the 4 products with regard to the amount of medication that gets into your blood and is available for your body to use

Regulatory Authorities

PAREXEL

- Committee for Medical Research of The University of the Free State
- South African Medicines Control Council (MCC)
- Declaration of Helsinki



Information on the study medication

PAREXEL

- 4 different acamprosate calcium tablet products
- You will receive one of these 4 products during the treatment phase
- Dosage = 666mg per phase

  3 phases = 6 x 111mg

  1 phase = 2 x 333mg
- Acamprosate calcium- treatment of alcohol abuse, to abstain from alcohol



Dosage of Acamprosate Calcium

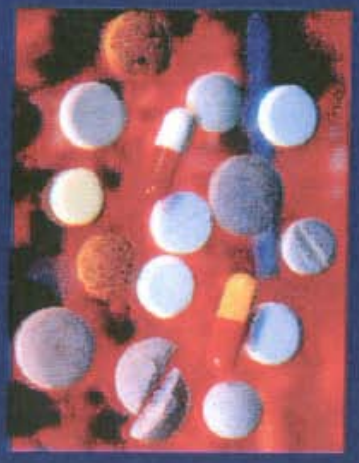
PAREXEL

USUAL DOSAGE

- 2 x 333mg 3 times daily

STUDY DOSAGE:

- 1 x 666mg in the morning per phase by mouth



Potential side-effects

PAREXEL

Body as a whole

- Accidental injury (including fractures),
- weakness,
- pain,
- headache,
- abdominal pain (stomach pain),
- back pain,
- infection,
- flu syndrome,
- chest pains,
- chills (feeling cold),
- suicide attempt



Potential side-effects

PAREXEL

Digestive system

- Diarrhea,
- flatulence (excessive gas in the stomach),
- nausea,
- vomiting,
- indigestion,
- constipation,
- lack of or increased appetite.

Potential side-effects

PAREXEL

Nervous system

- Anxiety (including nervousness),
- depression,
- dizziness,
- dry mouth,
- sleeplessness,
- sleepiness,
- paresthesia ("pins and needles", especially involving the face and extremities),
- decreased libido (decreased sexual drive),
- forgetfulness,
- thinking abnormal,
- quivering (shaking),
- vasodilatation (widening of the arteries),
- hypertension (high blood pressure).

Potential side-effects

PAREXEL

Skin and appendages

- Pruritus (itchiness),
- sweating,
- Rash

Cardiovascular system

- Palpitation (a sensation of feeling the heart beating rapidly),
- syncope (brief lapse in consciousness)

Potential adverse events

PAREXEL

Metabolic and nutritional disorders

- Peripheral edema (swelling of the extremities/lower limbs),
- weight gain

Muskuloskeletal system

- Myalgia (muscle pain),
- arthralgia (joint pain)

Special senses

- Abnormal vision,
- taste perversion (abnormal taste disorder)

Potential adverse events

PAREXEL

Respiratory system

- Rhinitis (inflammation of the mucous membranes of the nose),
- increased cough,
- dyspnea (shortness of breath),
- pharyngitis (inflammation of the throat),
- bronchitis (inflammation of the mucous membrane in the bronchial tubes)

Urogenital system

- Impotence (unable to achieve an erection)

Potential adverse events

PAREXEL

Less frequent and unexpected adverse events not mentioned above cannot be excluded.

Discuss any questions with your doctor

Allergic reactions

PAREXEL

Cannula may cause:

- Irritation
- Inflammation
- Clot formation



Contra-indications

PAREXEL

- patients who previously have shown hypersensitivity (allergic reactions) to acamprosate calcium or any of its ingredients,
- women who are pregnant or breastfeeding,
- patients with severe liver or kidney disease.



Study Performance

PAREXEL

Time	Phase 1	Phase 2	Phase 3	Phase 4
12 Hrs prior to dose	Report to study centre	Report to study centre	Report to study centre	Report to study centre
0 Hrs	Receive medicine	Receive medicine	Receive medicine	Receive medicine
48 Hrs	Discharge from study centre	Discharge from study centre	Discharge from study centre	Discharge from study centre
60 Hrs	Return to study centre for blood draw	Return to study centre for blood draw	Return to study centre for blood draw	Return to study centre for blood draw

14-21 Days Washout | 14-21 Days Washout | 14-21 Days Washout

Study Performance

PAREXEL

The following tests will be done upon admission:

- alcohol breath test and urine screen for drugs of abuse
- urine sample and blood samples, repeated 24hrs after dose and at the end of study
- body temperature, pulse rate and blood pressure, repeated before administration of medicine
- ECGs (cardiac tracings) before administration of study medication
- Pulse rate, blood pressure recordings and ECGs will be repeated at approximately 2, 4, 6, 24, 48 & 60 hours post-dose, and body temperature at 12 hours post-dose of Phases 1, 2, 3, and 4

Study Performance

PAREXEL

- receive the study medication at 07:30± with 240 mL water
- sit on your bed for 2 hours
- 4 mL (approximately 1 teaspoon) each, through a cannula (small plastic tube) inserted in a vein in your forearm
- If the cannula is removed, samples will be collected by venipuncture (drawing blood from a vein using a needle and syringe)
- Sixteen blood samples (64 mL) will be collected over 60 hours (i.e. each phase)
- Lab investigations before and after study = 95 mL (19 teaspoons)
- Total = will not exceed 351 mL (approximately 1.5 cups) (excluding repeats)

± The time of dosing commencement may vary due to logistical reasons.

Precautions and emergency measures

PAREXEL

- supervision for the first 48 hours after administration
- Should you experience any adverse events you will receive all the necessary medical treatment, even if the drug is withdrawn.

Restrictions

PAREXEL

Medicines (2 weeks prior before and during the study):

- Over the counter medicines (OTC)
- If you need any medication, please report it immediately to your doctor

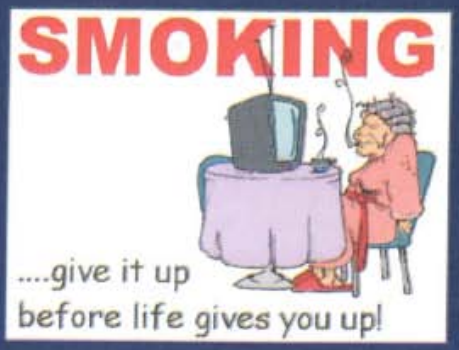


Restrictions

PAREXEL

Smoking:

- Only non-smokers will be included in the study.



Restrictions

PAREXEL

Diet:

3 Days before:

- fluids containing grapefruit

48 Hours before – 60 Hours after:

- methylxanthines e.g. caffeine

48 Hours before – end of study:

- No alcohol



Caution: Random alcohol tests may be done

Restrictions

PAREXEL

- fast from approximately 10 hours before dosing
- only food allowed: during first 14 hours of the first clinic day- standardised meals at 5 and 10 hours, and a standardised snack 13 hours after administration of study medication
- 240 mL water approximately 90 minutes before medication administration, with medication administration, 2 and 4 hours after medication administration and 240 mL apple juice with the meals.
- You will receive a caffeine-free warm beverage (200 mL) 8 and 13 hours after medication administration.
- All food and beverages will be caffeine-free
- From 14 hours after medication administration, you may eat and drink any food and beverages, except for food and fluids containing caffeine or xanthines, which will not be allowed for the entire clinic stay (up to 48 hours post-dose) and grapefruit and/or alcohol

Restrictions

PAREXEL

Physical exercise

- 24 hrs prior to administration
- 60 hrs post administration



FREQUENTLY USED CAFFEINE-CONTAINING FOOD AND BEVERAGES

PAREXEL

Not allowed 24 hours prior and 384hrs after administration:

- Coffee
- Tea
- Cola-flavoured drinks (e.g. Coke®)
- Cocoa
- Chocolate
- Caffeine-containing beverages (e.g. Red Bull®)







STUDY COMPLETION

PAREXEL

- Within 72 hours of completion of the last phase of the study
- A physical examination and urinalysis as part of the post-study safety evaluation
- ECG if your post-study visit does not coincide with a 60 hour visit
- If certain laboratory investigations (haematological or clinical chemistry) have to be repeated, the project nurse will set a date and time for repeat tests
- If you are withdrawn from the study, a post-study physical examination and other investigations may be performed



Withdrawal Criteria

PAREXEL

You have the right to withdraw from the study at any time, irrespective of the reason, without detriment to your medical care.

The following are pre-defined incidents that may lead to your withdrawal from the study:

- Adverse events as a result of taking the study medication
- Illness requiring medication
- Protocol violation (wilful disobeying of the protocol instructions and restrictions, as communicated to you both verbally and in this document)
- Abnormally raised body temperature before administration of study medication on clinic days
- Positive testing for pregnancy
- If any of the alcohol breath tests test positive, further participation in the study will not be permitted

Remuneration

PAREXEL

- No cost implications on you for study procedures
- Loss of time and inconvenience as a result of participation
- No remuneration is applicable to the screening procedures
- If you do not complete: compensation proportional to time of participation.
- R9 400.00 (taxable)
- Violation of the protocol instructions: may result in forfeiture of remuneration (wilful disobeying of instructions communicated to you verbally and in writing)



CONDITIONS OF INSURANCE COVERING CLINICAL STUDIES *(IN COMPLIANCE WITH ABPI GUIDELINES)*

PAREXEL

- Insurance coverage: Santam limited, policy No. P00931
- Indemnification is provided without regard to the question of legal liability as long as it can be shown that participation in the study caused the death or disability.
- The insurer will determine the amount of money necessary to cover the difference between the actual financial status if neither death nor deterioration in health occurred and the resulting financial status. Any compensation received from social insurance schemes or other sources will be deducted from the amount of compensation provided through FARMOVS-PAREXEL.
- During the course of the clinical study you may not participate in any other study.
- Any deterioration in your health during or directly after the clinical study must be reported to the doctor at once. In the case of a serious adverse event, the doctor must notify the sponsor, Ethics Committee and the South African Medicines Control Council by telephone or facsimile within 24 hours of becoming aware of the occurrence of the event. The notification must be followed by a written report within 48 hours after the initial notification, or at the latest on the following working day. FARMOVS-PAREXEL will inform the insurance company in the event of a claim.
- Should you have to receive any medical care not pertaining to the study in question, this must be reported to the doctor.

Additional Information

PAREXEL

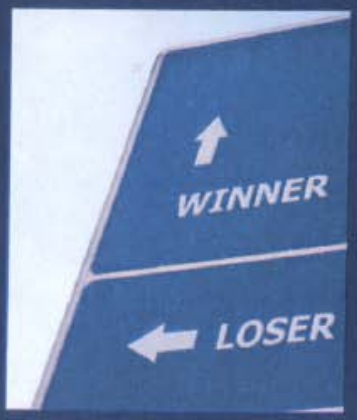
- 36 male volunteers
- Duration: 9-12 weeks



Benefits

PAREXEL

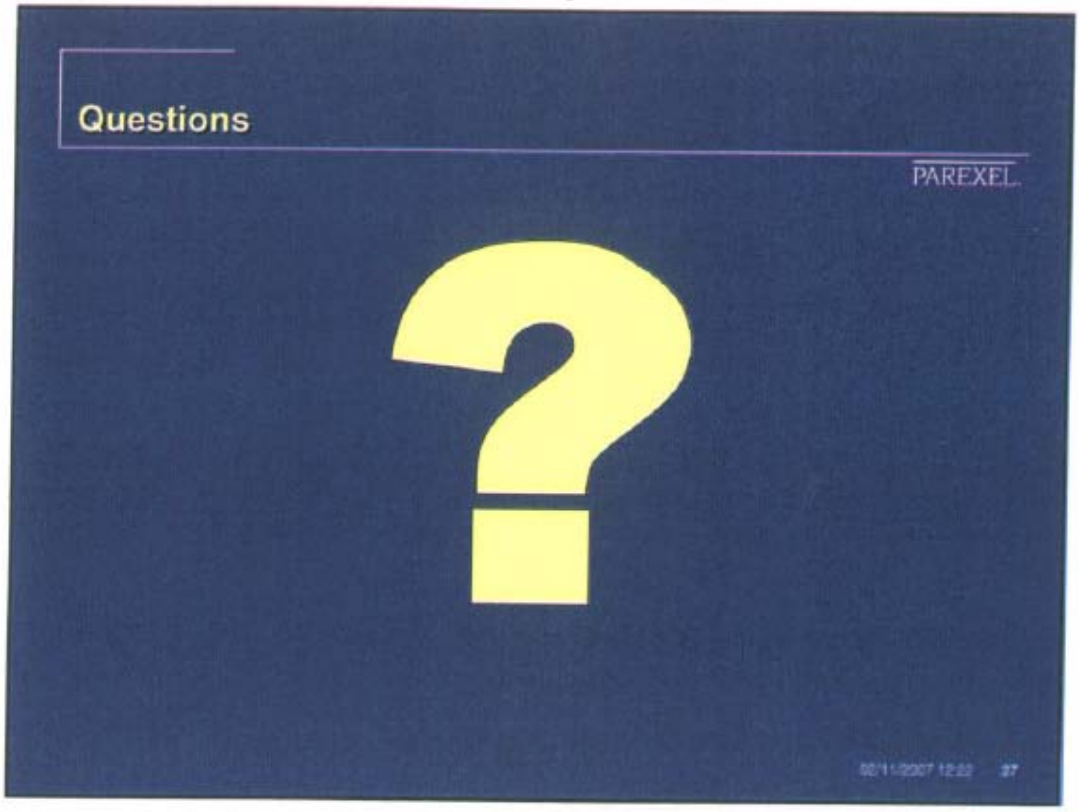
You will not benefit directly from this study- only HEALTHY participants enrolled



Confidentiality

PAREXEL

- Staff of FARMOVS-PAREXEL, the sponsor, and members of the Ethics Committee as well as the regulatory authorities will have access to all personal data pertaining to the study
- ALL findings: strictly confidential
- Data may be reported in scientific journals/meetings, but you will not be identified
- You will be informed in a timely manner when new information becomes available that may influence your willingness to continue participation in the study


Questions
PAREXEL
?

APPENDIX III: Study Specific Informed Consent Document

AN OPEN-LABEL, 4-WAY CROSSOVER BIOAVAILABILITY STUDY TO COMPARE THREE DIFFERENT FORMULATIONS OF ACAMPROSATE CALCIUM 666 mg (6x111mg tablets) WITH BESOBRIAL® 666 mg (2x333mg tablets) IN HEALTHY VOLUNTEERS

SCREENING PROCEDURE FOR INCLUSION IN A FARMOVS-PAREXEL CLINICAL STUDY

SUBJECT INFORMATION SHEET AND STATEMENT OF INFORMED CONSENT No. 1

(a copy of this is retained by the subject)

THE FOLLOWING PROCEDURES WILL BE PERFORMED ON YOU TO DETERMINE WHETHER OR NOT YOU ARE ELIGIBLE TO PARTICIPATE IN A CLINICAL STUDY

Height and mass measurements
Urine test
Urine screen for drugs of abuse
Alcohol breath test
Blood pressure, pulse rate and body temperature observations
Electrocardiogram (ECG)
Chest X-Ray
Laboratory investigations: Full blood count, clinical chemistry profile and HIV (Human Immunodeficiency virus) (the virus that causes AIDS), hepatitis B and C tests.
A full medical history and information on alcohol and tobacco consumption will be obtained from you and a physical examination will be performed on you.
If you fulfil the inclusion criteria of a specific study, do not meet any of the exclusion criteria and have given prior written informed consent for screening and phase-related procedures, you will be eligible to participate in the study.

DRUGS OF ABUSE TEST INFORMATION

You will not be included in the study in the event of a positive test result. A positive test result may be repeated once at the discretion of the study doctor.

HIV AND HEPATITIS B AND C INFORMATION

We need your consent to take a blood specimen to test for HIV and Hepatitis B and C antibodies. The results of these tests will determine whether you may participate in the study. Any disease from which you may be suffering might cause symptoms and signs that could be mistaken for adverse events due to the study medication, rendering the study results worthless. The study medication could, of course, also dangerously aggravate any condition, such as HIV or Hepatitis of which you may not be aware.
Although you may fear the consequences of a positive test, such as rejection by friends, wife, husband or employer, there are many advantages associated with knowing your HIV and Hepatitis status. These advantages include speedy commencement of therapy and counselling, and prevention of infection of friends, sexual partners or newborns.
Should your HIV or Hepatitis tests be positive you will be personally informed by the study doctor or an appropriately qualified designee and you will be referred to specialists for counselling and therapy. The matter as a whole will be treated as strictly confidential.
You are invited to discuss any matter requiring clarification with the study doctor before completion and signature of the consent form below.

DO NOT APPLY FOR PARTICIPATION IN CLINICAL STUDIES IN ORDER TO HAVE AN HIV TEST

I, **(full names and surname)** _____,
hereby declare and agree:

1. To undergo the screening procedure as described above to determine my eligibility for participation in a clinical study.
2. To have blood taken for HIV and Hepatitis B and C testing to establish my fitness to participate in the clinical study.
3. That I have been counselled by a counsellor, _____, regarding the rationale for performing the blood tests and I had adequate opportunity to ask questions.
4. That I understand that I should not participate in the study if I have reason to believe that I am infected by HIV or Hepatitis B or C viruses.
5. That I understand that my participation in the study is not guaranteed, until all screening checks are found to be favourable.
6. That I understand that the results of the tests will be given to me in confidence.
7. To not participate simultaneously in another study with an experimental drug, where the last administration (of previous study drug) was within 8 weeks before the first administration of study medication.

My consent is given of my own free will and I realise that I may withdraw from the screening procedures at any time.

I give my consent that, should I be included in a study, the staff of FARMOVS-PAREXEL, the sponsor and members of the Ethics Committee as well as the regulatory authorities would have access to all personal data pertaining to the study. Should I withdraw or be withdrawn from the study, FARMOVS-PAREXEL may store my information in the company database and have access to my records for auditing purposes and for study closure. The data may also be photocopied and stored at FARMOVS-PAREXEL and the sponsor on condition that national legislature with respect to the protection of personal data is adhered to.

I have received a copy of the Subject Information Sheet and Statement of Informed Consent No. 1.

Signature of subject _____ Date ___ ___ (d d) ___ ___ (m m) ___ ___ (y y)

Time ___ : ___

Signature of study doctor _____ Date ___ ___ (d d) ___ ___ (m m) ___ ___ (y y)

AN OPEN-LABEL, 4-WAY CROSSOVER BIOAVAILABILITY STUDY TO COMPARE THREE DIFFERENT FORMULATIONS OF ACAMPROSATE CALCIUM 666 mg (6x111mg tablets) WITH BESOBRIAL® 666 mg (2x333mg tablets) IN HEALTHY VOLUNTEERS

PAREXEL No.: 84172

SUBJECT INFORMATION SHEET No. 2

(a copy of this is retained by the subject)

If you have any questions about the study or need unfamiliar words explained to you, please ask a member of the clinical team.

INTRODUCTION

You are invited to take part in a clinical research study, sponsored by Somaxon Pharmaceuticals, Inc. Your participation in this study is voluntary. It is your right to withdraw from the study at any time without detriment to your medical care. If you decide to withdraw from the study, you are requested to inform FARMOVS-PAREXEL about the decision. Should you decide to participate in this study, you must agree to obey the instructions of the doctor. The doctor may withdraw you from the study for clinical reasons, or when you wilfully disobey the protocol instructions, summarised in this document, which have been communicated to you verbally and in writing. If you withdraw or are withdrawn from the study by the doctor, for whatever reason, after having taken the study medication, you will be requested to undergo the post-study laboratory investigations.

The purpose of this document is to inform you about the policies and procedures to be followed, your rights as a participant, potential benefits and risks, and basic rules according to which this study will be conducted. The study may involve unforeseeable risks.

PURPOSE OF THE STUDY

This is a research study to compare the blood levels and the safety of four different preparations of a medicinal product meant for use in human beings. One preparation is a proven remedy for alcohol abstinence and is already in extensive use (Reference product) and the other three are new preparations being sought to be freshly introduced into use (Test product). All the preparations contain the same active ingredient. The purpose of this study is to compare the four products with regard to the amount of medication that gets into your blood and is available for your body to use (bioavailability).

REGULATORY AUTHORITIES

The study was approved by the Ethics Committee for Medical Research of The University of the Free State and the South African Medicines Control Council. The study will be performed in accordance with the Declaration of Helsinki regarding recommendations guiding physicians in biomedical research involving human subjects (Tokyo, 2004), a copy of which may be obtained from the doctor should you wish to review it.

INFORMATION ON THE STUDY MEDICATION

The study medication consists of four different acamprosate calcium tablet products. You will be randomly assigned to receive one of the four products during a treatment phase. The dosage of acamprosate to be administered per treatment phase will be a total of 666 mg. However, you will receive 6x111 mg tablets in three of the phases and 2x333 mg tablets in the other one.

Acamprosate is used in the treatment of alcohol abuse as an aid in abstaining from alcohol. The recommended dosage is two acamprosate calcium 333 mg tablets taken three times daily. The dosage of acamprosate calcium which you will receive in this study will be a single morning dose of 666 mg (2x333 mg or 6x111 mg tablets) per treatment phase, administered by mouth.

POTENTIAL ADVERSE EVENTS

The following list contains adverse events which occurred in clinical trials, including those that occurred more frequently in subjects receiving acamprosate calcium (more than 3% more) than those receiving placebo, as well as frequent (defined as occurring in ≥ 1/100 subjects) treatment-emergent adverse events:

Body as a whole

Accidental injury (including fractures), weakness, pain, headache, abdominal pain (stomach pain), back pain, infection, flu syndrome, chest pains, chills (feeling cold), suicide attempt.

Digestive system

Diarrhea, flatulence (excessive gas in the stomach), nausea, vomiting, indigestion, constipation, lack of or increased appetite.

Nervous system

Anxiety (including nervousness), depression, dizziness, dry mouth, sleeplessness, sleepiness, paresthesia ("pins and needles", especially involving the face and extremities), decreased libido (decreased sexual drive), forgetfulness, thinking abnormal, quivering (shaking), vasodilatation (widening of the arteries), hypertension (high blood pressure).

Skin and appendages

Pruritus (itchiness), sweating, rash

Cardiovascular system

Palpitation (a sensation of feeling the heart beating rapidly), syncope (brief lapse in consciousness)

Metabolic and nutritional disorders

Peripheral edema (swelling of the extremities/lower limbs), weight gain

Muskuloskeletal system

Myalgia (muscle pain), arthralgia (joint pain)

Respiratory system

Rhinitis (inflammation of the mucous membranes of the nose), increased cough, dyspnea (shortness of breath), pharyngitis (inflammation of the throat), bronchitis (inflammation of the mucous membrane in the bronchial tubes)

Special senses

Abnormal vision, taste perversion (abnormal taste disorder)

Urogenital system

Impotence (unable to achieve an erection)

Less frequent and unexpected adverse events not mentioned above cannot be excluded. Additionally, the cannula inserted in a vein in your forearm for the collection of blood samples can lead to superficial irritation of the vein, inflammation or clot formation.

If you do not understand any of the above-mentioned adverse events or need any clarification about them you can discuss this with the study doctor.

You will not necessarily experience the adverse events as explained above at this dosage.

CONTRA-INDICATIONS

Acamprosate calcium is contraindicated (should not be used) in patients who previously have shown hypersensitivity (allergic reactions) to acamprosate calcium or any of its ingredients, in women who are pregnant or breastfeeding, and in patients with severe liver or kidney disease.

STUDY PERFORMANCE

The study will consist of four treatment phases and each will include a period of blood sampling of 60 hours which will start with a 48-hour clinic day at the research clinic. The administration of study medication on clinic days will be separated by periods without any treatment of between 14-21 days.

You will be admitted to the research clinic approximately 12 hours before dosing, and will remain in the clinic for 48 hours after administration of study medication. On admission to the clinic, an alcohol breath test and urine screen for drugs of abuse will be performed on you. If either of these tests are positive, you will not be allowed further participation in the study. A urine sample and blood samples will be collected, and these tests will be repeated 24 hours after ingestion of study medication and after conclusion of all other study procedures, to confirm your safety. Your body temperature, pulse rate and blood pressure will be recorded on admission and before administration of study medication on clinic days. ECGs (cardiac tracings) will also be collected before

administration of study medication. Pulse rate, blood pressure recordings and ECGs will be repeated at approximately 2, 4, 6, 24, 48 & 60 hours post-dose, and body temperature at 12 hours post-dose of Phases 1, 2, 3, and 4. After voiding and collection of a blood sample, you will receive the study medication at 07:30* with 240 mL water. Thereafter you will be requested to sit on your bed for 2 hours, whereafter you may move around.

Blood samples, 4 mL (approximately 1 teaspoon) each, will be collected through an indwelling cannula (small plastic tube) inserted in a vein in your forearm. The registered nurse will decide when to remove or replace the venous cannula based on the time (since insertion of the cannula) or if clotting occurs. If the cannula is removed, any subsequent blood samples will be collected by venipuncture (drawing blood from a vein using a needle and syringe). Sixteen blood samples will be collected over 60 hours. You will be asked to report to the research clinic for the blood sampling 60 hours after administration of study medication.

Blood samples will be collected relative to the time of administration of study medication to you (16 samples for each period of blood sampling; blood volume for each period of blood sampling = 64 mL (16 teaspoons); blood volume for laboratory investigations before and after the study = 95 mL (19 teaspoons); total blood volume to be collected during the study will not exceed 351 mL (approximately 1.5 cups), excluding required repeat laboratory investigations). Except for bladder voiding, you will remain sitting until 2 hours after administration of study medication, after which no restrictions concerning posture or movement will apply, and you will be allowed to get up and have freedom of movement within the confines of the clinic and recreation hall.

PRECAUTIONS AND EMERGENCY MEASURES

You will be under supervision for the first 48 hours after administration of study medication. Should you experience any adverse events you will receive all the necessary medical treatment, even if the drug is withdrawn.

RESTRICTIONS

You are requested to comply with these restrictions during the study period:

Medicines: You are requested not to use any medicines, including those sold over the counter, for two weeks before the first administration of study medication and for the duration of the study. If you need any medicine, you must immediately report it to the doctor.

Smoking: Only non-smokers will be included in the study.

Diet: You are requested not to eat or drink food and fluids containing grapefruit for three days before the first medication administration and for entire duration of the study. The ingestion of food and beverages containing methylxanthines e.g. caffeine will not be allowed for 48 hours before the start of each clinic day until 60 hours after administration of study medication. Alcohol will not be allowed from 48 hours prior to first dosing, until the end of the study. Alcohol breath tests will be performed on you at screening and upon admission to the research clinic, as well as for the post-study assesment. If this test is positive, you will not be allowed further participation in the study. You will be required to fast from approximately 10 hours before dosing. The only food allowed during the first 14 hours of the first clinic day will be standardised meals at 5 and 10 hours, and a standardised snack 13 hours after administration of study medication. You will receive 240 mL water approximately 90 minutes before medication administration, with medication administration, 2 and 4 hours after medication administration and 240 mL apple juice with the meals. You will receive a caffeine-free warm beverage (200 mL) 8 and 13 hours after medication administration. All food and beverages given to you during your confinement to the clinic will be caffeine-free. From 14 hours after medication administration, you may eat and drink any food and beverages, except for food and fluids containing caffeine or xanthines, which will not be allowed for the entire clinic stay (up to 48 hours post-dose) and grapefruit and/or alcohol which you will not be allowed to take for the entire duration of the study.

Physical activity: You are requested not to do any strenuous physical activity for 24 hours before each clinic day and until 60 hours after administration of study medication.

* The time of dosing commencement may vary due to logistical reasons.

FREQUENTLY USED CAFFEINE-CONTAINING FOOD AND BEVERAGES

Caffeine is present in food and beverages such as:

Coffee	Tea	Cola-flavoured drinks (e.g. Coke®)
Cocoa	Chocolate	Caffeine-containing beverages (e.g. Red Bull®)

You are requested to consult the labels on food products to determine if they contain alcohol and/or caffeine.

STUDY COMPLETION

Within 72 hours of completion of the last phase of the study or, if you do not complete the study, within 72 hours of withdrawal from the study, blood samples for the post-study laboratory investigations will be collected. A physical examination and urinalysis as part of the post-study safety evaluation, will also be performed on you (and an ECG if your post-study visit does not coincide with a 60 hour visit). Should it be found that certain laboratory investigations (haematological or clinical chemistry) have to be repeated, the project nurse will set a date and time, at your convenience, to report to the research clinic for follow-up blood samples to be collected. If you are withdrawn from the study, a post-study physical examination and other investigations may be performed on you at the discretion of the study doctor.

WITHDRAWAL CRITERIA

You have the right to withdraw from the study at any time, irrespective of the reason, without detriment to your medical care. The following are pre-defined incidents that may lead to your withdrawal from the study:

- Adverse events as a result of taking the study medication, at the discretion of the study doctor.
- Illness requiring medication. The decision whether or not to withdraw you will be at the discretion of the study doctor and will depend on the nature of the illness and medication used.
- Protocol violation (wilful disobeying of the protocol instructions and restrictions, as communicated to you both verbally and in this document), at the discretion of the study doctor.
- Abnormally raised body temperature before administration of study medication on clinic days.
- Positive testing for pregnancy.
- If any of the alcohol breath tests test positive, further participation in the study will not be permitted.

SUBJECT REMUNERATION

If you are included in the study, none of the study related procedures will have any cost implications on you. You will be remunerated for loss of time and inconvenience as a result of participation in the study. No remuneration is applicable to the screening procedures. If you do not complete the study you will be compensated proportionally for the time that you have already participated. If you complete the study you will receive R9 400 which is taxable. Violation of the protocol instructions may, however, result in forfeiture of remuneration. Protocol violation is defined as the wilful disobeying of instructions communicated to you verbally and in writing.

CONDITIONS OF INSURANCE COVERING CLINICAL STUDIES *(IN COMPLIANCE WITH THEASSOCIATION OF THE BRITISH PHARMACEUTICAL INDUSTRY [ABPI] GUIDELINES)*

1. Insurance coverage has been arranged to indemnify you of costs in the event of death or any deterioration in health or well-being caused by use of the study drug in the study.
2. Indemnification is provided without regard to the question of legal liability as long as it can be shown that use of study drug in the study caused the death or disability.
3. The amount of compensation should be paid appropriate to the nature, severity and persistence of the injury and will be within the terms and limits set forth in the insurance policy arranged by the sponsor.
4. During the course of the clinical study you may not participate in any other study. Any deterioration in your health during or directly after the clinical study must be reported to the doctor at once. In the case of a serious adverse event, the doctor must notify the sponsor, monitor, Ethics Committee and the South African Medicines Control Council by telephone or facsimile within 24 hours of becoming aware of the occurrence of the event. The notification must be followed by a written report within 48 hours after the initial notification, or at the latest on the following working day. FARMOVS-PAREXEL will inform the insurance company in the event of a claim.
5. Should you have to receive any medical care not pertaining to the study in question, this must be reported to the study doctor.
6. FARMOVS-PAREXEL will cover medical expenses (for example medication, consultation fees, hospitalisation) resulting from a drug-related adverse event or a drug-related bodily injury. This applies even if the study drug is withdrawn.

ADDITIONAL INFORMATION

Thirty-six male subjects will participate in this study.

The anticipated duration of the study is approximately 9-12 weeks. This will include: a screening visit within 15 days of the first administration of the study medication on the first clinic day, 4 clinic days (and blood sampling for 60 hours [3 days]) with periods without any treatment of 14-21 days between administrations of study medication on clinic days. Post-study physical examination and laboratory investigations will be performed within 72 hours (3 days) of completion of the last treatment phase. This does not include follow-up laboratory investigations that may have to be repeated should it be found necessary.

BENEFITS

You will not directly benefit from participation in this study as illnesses will not be treated and only healthy subjects will be included in this study.

CONFIDENTIALITY

Staff of FARMOVS-PAREXEL, the sponsor, and members of the Ethics Committee as well as the regulatory authorities will have access to all personal data pertaining to the study. All study findings will be handled in the strictest confidence. Data that may be reported in a scientific journal or presented at a scientific meeting will not include any information by which you can be identified.

You will be informed in a timely manner when new information becomes available that may influence your willingness to continue participation in the study.

In all cases of adverse events experienced, or for additional questions regarding the study, you can contact:

Name of doctor:	Tel:	Tel (after hours):	Cellular phone:
Dr A Mostert	051 410 3083	051 433 4844	082 495 2135
Dr F Burger	051 410 3090	051 522 2659	082 415 9497
Dr MM Ferreira	051 410 3061	-	082 491 6572
Dr PJ Jordaan	051 410 3162	051 441 8664	082 772 8134
Dr JH Potgieter	051 410 3091	051 522 0185	082 828 2949
Dr S Smith	051 410 3082	051 446 1382	082 463 8633
Dr J Terblanché	051 410 3029	051 436 4561	083 272 2718
Dr AM van der Bijl	051 410 3159	-	083 391 8345

FARMOVS-PAREXEL
Kampuslaan Suid
Campus of the University of the Free State
9301 BLOEMFONTEIN
SOUTH AFRICA
TEL: 051 410 3111 (Reception)
FAX: 051 444 3444 / 051 444 0975

Should you have any queries regarding ethical issues please contact:
The Ethics Committee of the Faculty of Health Sciences
Internal Post Box G40
Research Division
University of the Free State
9301 BLOEMFONTEIN
SOUTH AFRICA
TEL: 051 405 2812
FAX: 051 444 4359

If after you have consulted your doctor or the ethics committee and they have not provided you with answers to your satisfaction, you may write to the South African Medicines Control Council (MCC) at:

The Registrar
SA Medicines Control Council
Department of Health
Private Bag X828

PRETORIA
0001
FAX: 012 312 3105
E-MAIL: malemd@health.gov.za

STATEMENT OF INFORMED CONSENT No. 2

(a copy of this is retained by the subject)

I, **(full names and surname)** _____,
hereby agree to undergo the study procedures as explained in the Subject Information Sheet No. 2, and

I have been informed by the study doctor, Dr_____, concerning the purpose, procedures, restrictions, obligations, remuneration, insurance coverage and possible adverse events relevant to the study involved. I have been allowed adequate time to review the Subject Information Sheet and the Statement of Informed Consent.

My consent is given of my own free will and I realise that I may withdraw from the study at any time. I agree to inform FARMOVS-PAREXEL should I decide to withdraw from the study. Should I withdraw or be withdrawn from the study, FARMOVS-PAREXEL may store my information in the company database and have access to my records for auditing purposes and for study closure. I declare that I have made the necessary arrangements regarding the attendance of lectures and other academic activities with the lecturers concerned (if applicable).

I acknowledge that I understand the instructions relating to my participation in this study which have been communicated to me both verbally and in writing. I have been informed that disobeying the instructions may result in my exclusion from the study and forfeiture of the agreed remuneration.

I understand that a policy to cover subjects in clinical studies has been taken out by FARMOVS-PAREXEL, should disablement or death arise as a result of my participation in the study. I accept the conditions of the policy as set out in the subject information form. I will inform one or more persons (relative, close friend) of my participation in the study so that this person can inform the study doctor on my behalf in the event of my becoming ill, being involved in an accident and/or being hospitalised.

I acknowledge that I have been informed that all information obtained during the course of the study will be handled as strictly confidential. Data that may be reported in a scientific journal or presented at a scientific meeting will not include any information that will identify me as a subject in this study.

I give my consent that, should I be included in the study, the staff of FARMOVS-PAREXEL, the sponsor, and members of the Ethics Committee as well as the regulatory authorities would have access to all personal data pertaining to the study. The data may also be photocopied and stored by FARMOVS-PAREXEL and the sponsor on condition that national legislature with respect to the protection of personal data is adhered to.

I understand that I will be informed in a timely manner when new information becomes available that may influence my willingness to continue participation in the study.

I have received a copy of each of the following documents:

- Subject Information Sheet No. 2
- Statement of Informed Consent No. 2

I have received an information letter addressed to my general practitioner regarding my participation in this study. I undertake to forward this letter to my general practitioner.

Signature of subject _____ Date ___ ___ (d d) ___ ___ (m m) ___ ___ (y y)

Time ___ : ___

Signature of study doctor _____ Date ___ ___ (d d) ___ ___ (m m) ___ ___ (y y)

APPENDIX IV: WHEC Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Jacobs

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M070529**
PROJECT	Informed consent methods: an analysis of volunteer understanding
INVESTIGATORS	Ms J Jacobs
DEPARTMENT	School of Pharmacy
DATE CONSIDERED	07.05.25
DECISION OF THE COMMITTEE*	APPROVED UNCONDITIONALLY

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 07.06.04 **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr G Lowndes

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX V: UOFS Ethics Committee Approval

UNIVERSITEIT VAN DIE VRYSTAAT
UNIVERSITY OF THE FREE STATE
YUNIVESITHI YA FREISTATA

Direkteur: Fakulteitsadministrasie / Director: Faculty Administration
Fakulteit Gesondheidswetenskappe / Faculty of Health Sciences
Research Division
Internal Post Box G40
☎(051) 4052812
Fax nr (051) 4444359
E-mail address: gndkhs.md@mail.uovs.ac.za

Ms H Strauss

2006-10-26

MS J MOLLER
BAYER HEALTHCARE
PRODUCT DEVELOPMENT
27 WRENCH ROAD
ISANDO
1600

Dear Ms Moller

ETOVS NR 178/06
RESEARCHER: MS J MOLLER
PROJECT TITLE: INFORMED CONSENT METHODS: AN ANALYSIS OF VOLUNTEER UNDERSTANDING.

You are hereby kindly informed that the Ethics Committee approved the above-mentioned study at their meeting held on 24 October 2006 on condition that the Informed Consent is available in the language the trial person prefers.

Your attention is kindly drawn to the following:

- A progress/final report have to be submitted after completion of the study or within a year after approval of the project
- That all extentions, amendments, serious adverse events, termination of a study etc have to be reported to the Ethics Committee
- These documents have been accepted as complying with the Ethics Standards for Clinical Research based on FDA, ICH GCP and Declaration of Helsinki guidelines as well as the Clinical Trials Guidelines 2000: Dept of Health RSA and MRC Guidelines on Ethics for Medical Research

Will you please quote the Etovs number as indicated above in subsequent correspondence to the secretariat.

Yours faithfully

DIRECTOR: FACULTY ADMINISTRATION

339, Bloemfontein 9300, ☎ (051) 405 3013, 401 2847, (051) 444 3103, gndklt.md@mail.uovs.ac.za
Republiek van Suid-Afrika, Republic of South Africa