# THE DEVELOPMENT OF A GOOD CLINICAL PRACTICE TRAINING MODEL FOR USE IN SOUTH AFRICAN CLINICAL TRIALS

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**The Dissertation Submitted In Fulfillment Of The Requirements For The Degree Of Doctor Philosophy In The Department Of Nursing, Faculty Of Community And Health Sciences, University Of Western Cape.**

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## KEY WORDS

Good Clinical Practice (GCP)

Training model

Clinical Researcher

Clinical investigator

Study co-ordinator;

Adverse event

Trial subject

Clinical trial

Investigational drug

Standard Operating Procedure (SOP)

Training needs instrument.

Model

# ABSTRACT

**THE DEVELOPMENT OF A GOOD CLINICAL PRACTICE**

**TRAINING MODEL FOR USE IN SOUTH AFRICAN CLINICAL**

**TRIALS**

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Medicines for human use worldwide are generated in part through the conduct of clinical trials. This is done to ensure safety and efficacy. The involvement of human subjects in drug trials has raised concerns for the protection of human rights, as shown in United States' 1930 Traskegie and Thalidomide studies; the Nazi-Germany Studies of 1940 and the recent South African Wits University, Bezwoda Study of 1999. As a consequence of the medical misadventures, the Declaration of Helsinki was formulated in 1964 and revised up to 2002. Today, the International Conference of Harmonisation of Good Clinical Practice (ICH GCP) of 1996 guidelines are used worldwide (including the South Africa) in the conduct of clinical trials.

The focus of this study is on development of a Good Clinical Practice (GCP) training model for clinical researchers. The clinical researchers are comprised of study co-ordinators and clinical investigators (principal investigators and sub-investigators). The flow of this study is guided by the systems theory. The writer had to start by exploring the clinical researchers' knowledge base and training needs, using the research instrument that was developed in this study. This approach is supported by literature that emphasises the fact that the ideal training model should be preceded by the assessment of training needs of people that will be using it so as to ensure that it's content addresses the needs of the people it is designed for.

The study took place in South Africa. The objectives of the study were to first develop an instrument to be used in identifying the current GCP knowledge and training needs of clinical researchers; secondly identify the knowledge level and training needs using the designed instrument and thirdly, based on the findings, develop a GCP training model so as to facilitate the achievement of quality standards for the conduct of clinical trials in South Africa.

The sample of 100 participants was from all clinical researchers in South Africa. Experts in the field of GCP and clinical trials gave input on all stages of the study. The stages are research instrument development, assessment of training needs and development of a GCP training model.

Instrument development: this formed the corner stone of this project. The instrument was drawn up because there was no specific instrument available. The instrument for this study was developed based on data gathered from the previous studies conducted on related topics which included ethical issues, informed consent, quality assurance in clinical trials, previous audit findings from previous clinical trials

and patients' safety. Literature reviewed gave additional guidance for the development of an ideal instrument. Five Key informants were from the Ethics Committees, Universities, Medical Research Council (MRC) and the Department of Health. The instrument was designed in such a way that it was going to show the knowledge level based on the score calculated by grouping some knowledge specific questions. The instrument was pre-tested on six clinical researchers before finalisation.

Out of 100 randomly selected clinical researchers, 84 completed the needs assessment instrument. The writer collected the data in person. After collection of the data, the responses were grouped, coded and entered into an excel spreadsheet database. The data was then imported to Stata statistical package for multivariate statistical analysis. The results showed that about 50 % of respondent achieved less than 50% of the total knowledge score in areas that included informed consent, source data verification including writing of source notes for the patients on clinical trial, investigator responsibility, study agreements, patient safety, quality assurance, clinical data handling and the provisions of the South African Guidelines (2000) on conduct of clinical trials. The GCP training model was developed based on the survey results, literature on training model development, previous clinical research studies and audit findings, key informants input, both ICH GCP and South African Department of Health Guidelines, Outcome Based Education (OBE) and Adult Education Principles. Further field-testing of the training model is recommended.

# DECLARATION

I declare that this study is my own original work. It has not been submitted before for any Degree or examination in any other university. All sources that have been used or quoted have been indicated and acknowledged as complete references.

Nomusa Joyce Raphesu

September 2005



Signature ……

## DEDICATION

This work is dedicated to my family and Christian Faith Fellowship (Germiston) church members who were supportive during hard times, whilst I was busy with my studies.

To my two sons, Nkululeko and Manqoba who were very helpful and supportive during my studies. They should grow to reach similar heights and even go beyond this point.

To my late mother: Happy Nxumalo and my late grand-mother: Flora Nxumalo, an ex-teacher who has been a mentor, throughout until she passed out.

To all the Nxumalo family, for the prayers and support during hard times. MaNdwandwe, Keep it up!

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The key informants with their contribution towards research instrument development and GCP training model development.

The MRC Senior Statistician, Dr. Jonathan Levin who helped from the early stages of the study until the end. This included guidance and supervision on sampling and sampling methods, data collation, grouping, cleaning, importation from excel to Stata, data analysis and interpretation of results. To UWC Statistician, Dr T. Kotze who helped me finalise the study.
Some of my colleagues, with support and ideas during hard times.

I further acknowledge the employment opportunity, to the field of clinical research from 1994 up to date. I have gained GCP exposure and experience in this field at both international and local level, including the way to conduct and manage clinical trials.

The library staff from UWC, Wits and Natal Universities for all the support and guidance with literature search.

The UWC support faculties which include the Writing Skills Centre, Noluthando Sihlezana and Climmie Marree for technical arrangement of the dissertation.

My Supervisor, Professor Elma Kortenbout, the most important person that has shaped the whole work into a good piece of work that you are going to read. Lastly, but not least, God Almighty, that gave me strength and guidance to do this study up to this point.

## ABBREVIATIONS

GCP: Good Clinical Practice

CRF: Case Report Form

SOP: Standard Operating Procedure

DRF / DCF: Data Record Form / Data Clarification Form (also called data queries)

MCC: Medicines Control Council

IRB: Independent Review Board same as Independent Ethics Committee (IEC)

LOG: Local Operating Guidelines

ICF: Informed Consent Form

PIL: Patient Information Leaflet

SDV: Source Data Verification

OBE: Outcome Based Education

SKAV: Skills, Knowledge, Attitude and Values

CRA: Clinical Research Associate (also called monitor)

AE: Adverse Event

SAE: Serious Adverse Event

ICH: International Conference on Harmonisation

FDA: Food and Drug Administration Board

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# CHAPTER 1

## 1.1 Introduction

The world is dependent on medicines for which safety and efficacy has been established. The controlled clinical trial is the mechanism required by drug regulatory authorities across the world through which this evidence is generated and upon which the decision to register a drug for use in clinical practice is made (Raven, 1993).

The primary focus of this dissertation is to develop a training model for clinical researchers and essential study support staff (study coordinators) based on international guidelines of good clinical practice (GCP). This will comprise three stages: (1) the development of a research instrument, and (2) exploring the training needs expressed by clinical researchers. The training needs will be assessed through the use of a developed research instrument, an accepted approach (Murk, Barrett, & Atchade, 2000) in which identification of educational needs from clinicians in the field, is proposed as the method of choice, for developing an ideal training model. The final, third stage will be the development of a GCP training model.

## 1.2 Background

Many clinical trials are conducted in South Africa due to the nature of the population, the various disease patterns and the medicines that are being developed (Department of Health, 2000).

Good Clinical Practice originated in the United States of America. The first published recommendations were published in 1977 and served as the first GCP guide (to investigators and the pharmaceutical industry undertaking clinical trials in the United States (Raven, 1993).

Following this, GCP guidelines were developed and implemented across Europe, and subsequently throughout the world. These guidelines now form the basis for drug regulatory laws in most countries. This process should have gone some way to allaying anxiety about the quality and reliability of the research data being submitted to regulatory authorities. The primary objective of GCP guidelines is to ensure that clinical trials are based on an adequate scientific rationale, are verifiable, monitored for proper conduct, are carefully documented, and comply with ethical guidelines. These requirements are set out primarily to ensure safety of research participants (Gual, 1998; Raven, 1993).

GCP exists to provide a framework for evaluating relative medico-legal risks and controversial issues such as putting patients on the study without getting informed consent, or even knowledge of being in the clinical trial that, may be implicit in the conduct of clinical trials. In South Africa, regulations set out by the Department of Health and the Medicines Control Council (MCC) to control the conduct of all drug development studies. Independent ethics committees are constituted in accordance with GCP guidelines and

are tasked primarily with the ethical aspects of study proposals. The Declaration of Helsinki is there to guide the clinical researchers in biomedical research involving human subjects. In spite of extensive control measures, the very nature of clinical trials will continue to hold a degree of risk both for participants and investigators, as the full range of treatment responses and adverse events can seldom be predicted in advance of studies on human subjects. As such a clinical trial requires prospective subjects to voluntarily expose themselves to an element of risk. GCP guidelines essentially seek to regulate and minimise these inherent risks.

South Africa has a population of approximately 43 million people (Population Statistics, 2000). It is difficult to establish the percentage of the sick population due to the rising number of illnesses caused by the HIV epidemic. Presently, approximately 183 pharmaceutical companies are registered within South Africa (Pharmaceutical Medical Association, 2000).

These local representatives of invariably larger multinational corporations are the primary drivers behind clinical trials. Their strong presence in developing countries has frequently exposed these companies to criticism in respect of their recruitment policy in which they are accused of exploitation of potentially vulnerable subjects by virtue of their limited access to new and frequently expensive drugs, adverse events and the failure to obtain real informed consent (Carte Blanche, 2001).

A GCP training model for clinical researchers will seek to ensure that clinical trial staff is equipped with the requisite knowledge and ability to conduct clinical trials. The researcher was stimulated to examine this topic because all medicines and /or medicinal products that are on the market, are first researched and tested before being made available for public use. The clinical trials are then designed to establish the safety and effectiveness of medicines, before they get licensed for use by various individuals or made available in an open market, depending on the schedule of the medicine (Medical Research Council (MRC) Guidelines, 1998; Heilman, 1995; Raven, 1993).

Considering the high level of clinical trial research in South Africa in conjunction with the fact that GCP guidelines have been developed (Department of Health, 2000), it seems important to establish the level of knowledge of GCP in order to identify shortcomings when compared to both international and South African guidelines. This information will form the basis for the development of a training model that complies with requirements contained in published GCP guidelines, while addressing the identified shortcomings in GCP knowledge and training needs identified in phase 2 of the study.

## 1.3 Significance of the Study

Developing a new drug is both an expensive and lengthy process, that can take up to 15 years, and could cost up to 15 million US dollars (WHO, 1994). For these reasons, adequately equipped personnel are essential to the process of acquiring high quality data with which application for registration is made.

Since this study aims to develop a model for training in GCP for clinical researchers, the first step (step one) is to develop an instrument that will be used to explore the GCP knowledge-base and training needs of an existing pool of clinical researchers (step 2). This will provide the foundation from which the researcher will develop a training model in phase three (Murk, Barrett & Atchade, 2000; Stufflebeam, 1971). If possible, this will proceed to have accreditation (stage 4) and finally implemented (stage5) (See figure 2.1).

## 1.4 Problem Statement

Regulations imposed on the process of drug development to the point of bringing a new compound to market demand that clinical trials be conducted on human subjects. The success of this process depends to a large extent on the involvement of competent clinicians in the particular field of study. Present guidelines on GCP provide a framework from which

a knowledge base on the basic requirements of a clinical researcher can be developed.

Presently, however, it is not known to what extent this knowledge resides with clinical researchers and to what extent it is applied. This despite the avowed compliance with GCP guidelines required in all recently approved research proposals involving human subjects. Furthermore, to our knowledge no GCP training model based on international and local guidelines, is available in South Africa.

### 1.5 Purpose of the Study

The purpose of the study is to develop an instrument to identify the GCP training needs of clinical researchers. After the needs have been identified to develop a model for training in GCP that will be implemented on a trial basis.

### 1.6 Research Objectives

- To develop an instrument to identify the GCP training needs for clinical researchers.
- To establish the existing knowledge levels by measuring the training needs.
- To design a model for training in GCP for clinical researchers.

## 1.7 Theoretical Framework

### 1.7.1 The Systems Theory

The use of the systems theory to underpin this study is introduced here and expanded in chapter 2. A system is a set of objects or elements that interact to achieve a specific goal. This does not only include the set of objects / elements but the attributes of those objects / elements and the relationships between them. This is an ongoing process that may have diverse elements and interrelationships (Gillies, 1994; Putt, 1989; Arndt & Huckabay, 1980; Bossel, Klaczko & Muller, 1976).

In its broadest sense, Klir (1972) refers to the general systems theory as a collection of general concepts, principles, tools, problems, methods and techniques associated with a system. Klir (1972) argues that this requires the exploration of wholes and wholeness, the interdisciplinary nature of concepts, models and principles applying to the "system", and hence provides a plausible approach to the unification of science (Klir, 1972). Gillies, (1994) describes the essential elements of a system as being inputs, process/or output, controls, and feedback.

While all three understandings of system theory have undoubted merit, this researcher prefers a composite view in which a system is composed of units, sub-unit and elements that may vary in shape and

function, but execute their appointed functions in “consultation” with each other to ensure an optimal outcome for the system. Implicit in this view is that sub-units may function independently, while interconnectedness remains essential for achieving their common goal. As such, these sub-units cannot operate in a vacuum (independently) but within controlled systems, in part defined by the particular environment (Faurre & Depeyrot, 1977).

As such, South Africa forms the environment in which the conduct of clinical trials is the central theme (system) that exists in order to facilitate the eventual licensing of safe and effective medicines for use in clinical populations.

The elements / sub- units include the clinical researchers, research participants (healthy and sick) and individual clinical trials. The control for the system is provided by local and international GCP guidelines, regulations of the South African Department of Health and its Medicines Control Council and finally the ethical principles of research in human subjects contained in the Declaration of Helsinki (World Medical Association, 2000).

Institutional Review Boards (IRBs), also called Ethics Committees are tasked with the protection of subjects that are likely to participate in clinical trials. These tasks include ensuring the

completeness and accuracy of patient information and consent forms which are designed to ensure that patients are in a position to make informed decisions regarding participation in clinical trial research without coercion or threat of losing treatment opportunities should they elect not to participate.

The Trialists' Declaration of Intent (Annexure 9) binds signatories to comply with the approved study protocols and to conduct the clinical trial in accordance with ICH GCP Guidelines. Without the requisite knowledge of these guidelines and how to apply them in the context of a clinical trial, clinical researchers may expose research participants in situations that may constitute undue risk. From the above it becomes apparent that the effective functioning of this complex system depends on adequately connected, communicating and regulated systems. This systems approach is further summarized as input, throughput (process) and output also called outcomes (Department of Health, 2000; ICH GCP Guidelines, 1996; Gillies, 1994).

### 1.7.2 The System Input

In this study, the system input comprises the elements that contribute to the development of the research tool and the training needs based on the perceptions of the key informants. In addition, the input of the perceived training needs / requirements will be measured against GCP standards found in the ICH GCP 1996 (Raven, 1993).

The output following this exercise will inform what should be included in the planned need assessment tool.

### 1.7.3 The Throughput / Process

This is the process or series of actions by which the system converts energy input from the environment and its boundaries into products or desired services that are usable by the system or its environment (Gillies, 1994). In this study the process will entail application of the needs assessment instrument. The application will assist in the identification of training needs by defining deficits in knowledge base through the survey (study stage 2). In addition, throughput will include the design of the GCP training model (study stage 3) based on principles compatible with outcomes-based adult education.

### 1.7.4 The Output

Within the systems approach herein proposed, the final outcome of the system throughput is the product or service that emerges following the processing of technical, social, financial and human input. In stage 1 of the study, the output will comprise the research instrument that will be used to survey the training needs in stage 2.

Similarly, the output of phase 2 will comprise the survey results namely the identified training needs. In stage 3, the development of

the optimal GCP training model within the context (environment) of the perceived needs, when applied will provide the platform on which to develop an informed clinical researcher. Higher levels of competence in clinical researchers will promote safer environments within which clinical trials are conducted with potential benefit for credibility of results.

The strength of the systems approach lies in its reliance on an examination of the system as a whole without loss of attention to detail contributed by component sub-systems, As a result one is able to explore components as they occur individually as well as their relationship to the functioning of the system as a whole which may be variably prospective as well as retrospective. Gillies, (1994) emphasises the multidimensional nature of the system in which sub-units convert information, energy or material into a planned outcome or product for use in or outside the system (Gillies, 1994).

## 1.8 Definition of Terms

### 1.8.1 Good Clinical Practice (GCP)

This is a standard for design, conduct, performance, monitoring, auditing, recording and analyses of clinical trials. GCP ensures that the data and reported results are credible and accurate. In addition

GCP ensures that the rights integrity, and confidentiality of clinical trials subjects are protected (ICH Guidelines, 1996).

### 1.8.2 Training Model

Training involves providing instructions that with practice, further teaching and raising general awareness about levels of mental and physical efficiency (Sykes, 1982). A training model includes a descriptive plan that has documented a series of events and instructions directed towards a specified goal or change in behavior (operational definition).

### 1.8.3 Understanding

To understand means to know. To see the meaning of something, to have an impression of, or about something, to know why or how something is done in a particular way. Understanding may also be viewed as the "how", what is, the perception or creation of analogies and likenesses is the central function of all understanding of reality (Sinclair, 1995; de Jager, 1990; Mandison, 1982).

### 1.8.4 Clinical Investigator

A person with the requisite training and skill to conduct a successful clinical trial. A team of clinical investigators from a single site may act under the guidance of the lead or principal investigator and are designated sub/co – investigators (ICH Guidelines, 1996).

### 1.8.5 Study Co-coordinator

Any person working at a trial site, who co-ordinates or ensures smooth running of trial/s conducted by investigator(s) and/or research team. This position may only be filled by a person with a medical background (nurse, technologist, pharmacist or medical doctor).

### 1.8.6 The Clinical Researcher

Any person working at a clinical research site, conducting a clinical trial, be it a clinical investigator or a study co-ordinator, in this study this person will be addressed as the clinical researcher (operational definition).



### 1.8.7 Clinical trial

Any investigation involving human subjects that is designed to study any combination of clinical efficacy, pharmaco-kinetic, pharmaco-dynamic and adverse effects of an investigational product. The terms clinical study and clinical trial are used synonymously (ICH Guidelines, 1996).

### 1.8.8 Trial Participant

An individual who participates in a clinical trial, either as a recipient of investigational procedure or product(s), or as part of the control group (MRC, 1998; ICH Guidelines, 1996).

### 1.8.9 Standard Operating Procedure (SOP)

The detailed, written instructions to achieve uniformity of performance of a specific function or procedures. Usually the SOPs are country specific and may vary from company to company (ICH Guidelines, 1996).

### 1.8.10 Adverse Event and Serious Adverse Event

Any untowards medical occurrence in a patient or clinical investigation participant, administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. This includes any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidelines, 1996).

If the adverse event (a/e) becomes serious, or meets one of the listed criteria, this (a/e) becomes a Serious Adverse Event (SAE), and such occurrence at any dose should meet one of the following criteria:

- results in death
- is life threatening
- requires inpatient hospitalization
- prolongs hospitalization
- results in persistent or significant disability or incapacity
- leads to congenital anomaly or birth defect (ICH Guidelines, 1996).

### 1.9 The Structure of the Dissertation

**Chapter 1**: Introduction – provides the background, rationale and objectives of the study.

**Chapter 2**: Conceptual Framework – discusses the conceptual framework that locates this study within the overall system.

**Chapter 3**: Literature Review – presents the literature related to the conduct of clinical trials and Good Clinical Practice, the development of a research instrument and a training model.

**Chapter 4**: Research Design – Here the details of each of the study stages is outlined in detail. These include (1) research tool development, (2) survey of the GCP training needs and (3) development of a GCP training model. Details of a pilot study from which the survey questionnaire was refined are also provided a

guideline to ensure that the survey questions were clear and understood.

**Chapter 5**: Data analysis, results and initial interpretation of the survey data are provided.

**Chapter 6**: Summary and discussion of results is provided.

**Chapter 7:** The Proposed Training Model is presented based on the study results.

**Chapter 8**: The final training model is presented following review and incorporating the recommendations of key informants.

**Chapter 9**: Conclusion, future recommendations and limitations of the study are outlined here. .

## 1.10 Conclusion

This introductory chapter has described the area of study and sought to familiarise the reader with relevant terminology. The following chapter, (chapter2) will discuss the theoretical framework that has formed the basis of the direction of study and the emergent arguments in support of the proposed model.

# CHAPTER 2

## THEORETICAL FRAMEWORK

### 2.1 Introduction

Systems theory forms the theoretical basis on which this study is based and informs the chosen methodology.

### 2.2 Systems Theory

#### 2.2.1 Definition

A system is a set of objects or elements that interact to achieve a specific goal. This does not only include the set of elements but the attributes of those elements and their interrelatedness (Gillies, 1994). The sub-systems, or units of a system require special ordering, the result of which is a strong, yet diverse series of inputs that ultimately exist to advance system as a whole (Gillies, 1994; Putt, 1989; Arndt & Huckabay, 1980).

In the broadest sense, Klir (1972) refers to the general systems theory as a collection of concepts, principles, tools, problems, methods and techniques that can be associated with a particular system. As indicated earlier (chapter one), the system consists of exploration of wholes and wholeness, the interdisciplinary nature of concepts, models and principles as they apply to the system. This

provides an approach towards the unification of science or theory as proposed by von Bertalanffy (1972).

Gillies (1994), describes the elements of the system as those of: inputs; process/or output; controls & feedback. This is also explained as input, throughput / process and output / outcomes (Gillies, 1994; Putt, 1989).

### 2.2.2 Developmental History

The concepts of general systems theory, were first publicised in 1920s and eventually formalised in 1954 through the establishment of General Systems Research, an affiliate of the American Association for the Advancement of Science. In line with this, the American Psychiatric Association developed a task force to work on general systems theory and psychiatry. With time, systems thinking has transversed the theoretical sphere to areas of applied sciences including health sciences, and has incidentally informed much recent scientific thoughts (Putt, 1989).

The development of a systems theory was supported by a biologist (von Bertalanffy) in 1960s - 1970s, in which he identified a need for a single, systematic theoretical framework to account for the striking parallels found in different scientific disciplines. Von Bertalanffy, (1973) theorised on the existence of universal principles

and laws, regardless of their specific elements and goals. His theories support the wholeness, differentiation, progression, centralization, hierarchical order and equifinality of the system (von Bertalanffy, 1973).

The general systems theory encompasses principles generalisable to an array of otherwise distinct systems, including open and closed systems. This enables sharing of advances from different disciplines that contribute to the body of knowledge for general living as well as scientific and non-scientific use. Feedback systems facilitate communication within the subsystems and allow modifications and adjustments to be made to optimize system functioning in pursuit of a common output. Systems theory as described above will be applied to all phases of this study and with its flexibility, it will allow feedback and exchange of information during the conduct of the study (Gillies, 1994 & Putt, 1989).

## 2.3 Components of a System

### 2.3.1 The Environment

Each system is defined in relation to its environment, and the systems environment can be defined only with reference to the system and its boundaries. In short, it should be explained how the environment affects or influence the system and visa versa. The system environment comprises a set of objects, events or conditions

that although not an integral part of the system, have significant bearing on system functioning.

In this particular study, the researcher has set out to develop an instrument to be used in assessing study co-ordinators and investigators needs and deficiencies in GCP knowledge in relation to the professional conduct of clinical trials. South Africa is the (physical) environment in which this study is sited. As an independent state, particular rules and regulations exist within social and medical science circles. Control and regulatory responsibilities that fall to these communities create the specific environment within which clinical trials are conducted. GCP guidelines form a sub-system that provides the framework for standardisation in the conduct of clinical trials (Gillies, 1994).

### 2.3.2 The input

This is the energiser or operating material of the system and may be received from the environment and other systems. Input elements include goals, human resources and material resources. These elements interact to achieve the specified goals of both sub-systems and main system. In the present study some examples of the goals and elements include:-

- a primary goal of developing a GCP training model;

- a secondary goal of developing an instrument to be used in measurement of knowledge deficits and training needs;
- human resources comprise the clinical researchers and experts who will provide the essential data for input into the development of the training model,
- the developed instrument it self, as a component of input, yet it can also be viewed as an output within the input (Gillies, 1994).

### 2.3.3 Throughput

A series of actions through which the system converts input energy in part derived from the environment into products or the desired "service" for use by the system in achieving the end goal. In this study the researcher has viewed the application of the instrument as a throughput process.

Pre-testing the developed instrument before finalisation and getting expert opinions as well as the final development of the training model are components of the throughput. Pre-testing and expert opinion will contribute to the findings generated during the throughput phase, which are reliable and valid.

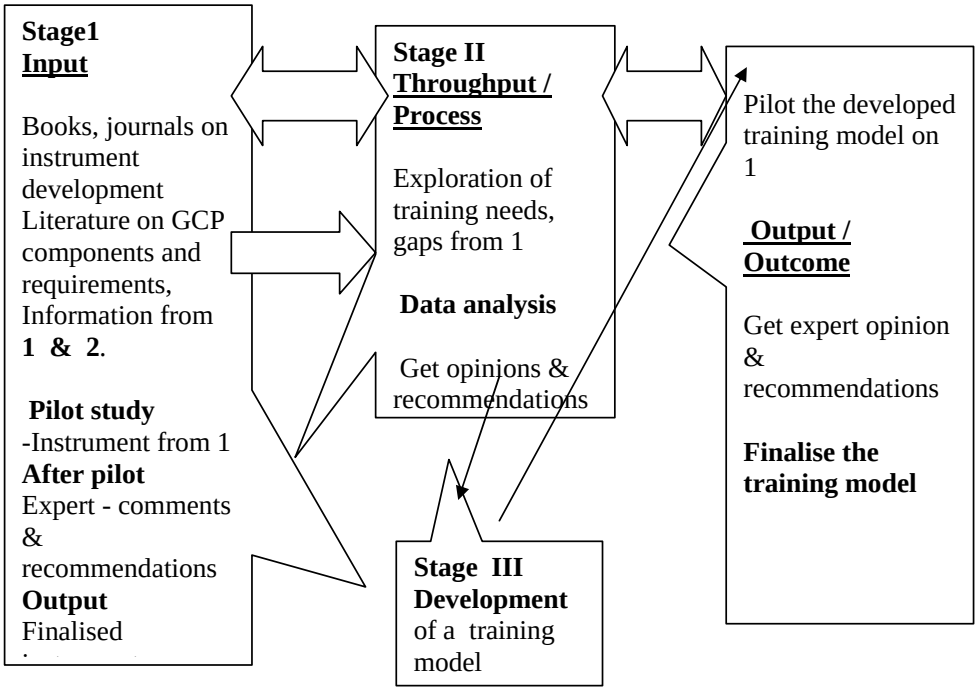
### 2.3.4 Output

The final outcome of the system throughput, namely: the product or service that emerges from the processing of technical, social, financial and human input, in this case, the training model.

## 2.4 Application

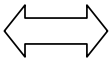
The application of the systems theory to the design of this research is given in figure 2.1:-

**Figure 2.1: Application of Systems Theory adapted from Gillies, 1994**




**Key:** 1= Clinical researchers

2 = Key Informants

 = Interrelationship between components leading to information exchange and feedback.

The advantages of this approach include the fact that it examines the system as a whole from all angles. It goes further to look into each sub-system, explores it both as individual component and in relation to the whole system. Further to this all interrelated factors that link the main system and subsystems are explored, then at the end a comprehensive outcome is concluded. It allows forwards and backwards exploration if the need arises. This is indicated by the arrows in the diagram (figure 2.1). Gillies, (1994) puts emphasis on the fact that the function of the system is multi-fold, part of which is to convert information, energy or material into a planned outcome or product for use within the system, outside the system or both (Gillies, 1994).



## 2.5 Conclusion

This chapter has outlined the theoretical framework: the systems theory that will be applied in this study. The researcher has shown how these theories will be used to direct the entire research process, and has highlighted the flexibility of this approach as an inherent strength that this study will seek to exploit.

# CHAPTER 3

## LITERATURE REVIEW

### 3.1 Introduction

The literature reviewed presented here focused on GCP (both international and local), its development, application, informed consent and the issues that pertain to the preparation of clinical researchers for GCP. From this reading, issues that emerge that are critical in the conduct of clinical trials in South Africa will be examined. These focus points are in part derived from previous clinical trial audit findings, local requirements for application to conduct clinical trials, and the specific responsibilities of local stakeholders and groups.

The control system in this context implies regulatory bodies including the Medicines Control Council, Ethics Committees and Medical Associations amongst others.

### 3.2 The History and Development of GCP

Many clinical trials are conducted in South Africa due to the nature of the population whereby the majority fits into the criteria of a vulnerable community as described by the Department of Health (2000), the various disease patterns and the various types of

medicines that are being developed (Department of Health, 2000; Gual, 1998).

Good Clinical Practice originated in the United States of America. This dates back to 1938 whereby the 1938 Food, Drug and Cosmetic Act was laid down.

The rash of severe birth defects attributed to the pharmaceutical thalidomide (1961-2) raised considerable concern around regulations related to safety in untested populations, in this case the unborn children of pregnant mothers. This also raised concerns as to whether proper informed consent was obtained from the pregnant women who participated in this study (www.ich.org/ich8.html -09/04/03).

In 1963 the Investigational New Drug Act (United States) was developed in response to the "Thalidomide" incident. This act aimed at controlling the steps to be followed when developing a new drug with special emphasis on safety of subjects (www.fda.gov/opacom/laws/cntrlsub/ctlsbtoc.htm.9/4/03;. www.ich.org/ich8.html - 9/11/03).

(http://www.fda.gov/oc/gcp/regulations.html - 30/11/03)

The Declaration of Helsinki first drafted in 1964, and most recently updated in 2000, to guide medical practitioners on the safe conduct of clinical trials and included areas such as intent to treat, (which binds the physicians into the commitment to treat patients, which goes beyond doing clinical research), as part of clinical trial conduct, were emphasized.

In early 1970s a set of proposals on safe conduct of clinical trials was prepared by the concerned parties which include physicians, World Health Organisation and ethical bodies, with a motivation to ensure safe conduct of clinical trials and means to ensure credible data. These proposals got approved in 1996 although formally published in 1997. The 1996 a meeting took place in South Africa in Cape Town and the aim of the meeting was to guide the investigators and pharmaceutical industries undertaking clinical trials, to do this correctly. These guidelines were published as Sponsor / Monitor Obligations Proposals and clearly stated what is expected from the sponsor (industry) and the CRA to take precautions in ensuring that the clinical trial subjects are protected (www.ich.org/ich8.html - 17/11/03).

(http://www.fda.gov/cvm/guidance/guide85 - 30/11/03)

The GCP guidelines to emerge from the lengthy development period, were then adopted across Europe. For the first time, a degree of standardised research practice now existed in Europe and North

America. The guidelines provided a framework from which regulatory authorities could for the first time appraise the scientific merit as well as the verifiability, quality of monitoring and study documentation of studies submitted for of registration of new products. These principles remain to this day and are enshrined in WHO regulations (1994).

Regulations around informed consent were first formulated in the United States in 1981, encompassed herein were the central principles of voluntary and fully informed consent prior to participation in a clinical trial (ICH GCP, 1996; Raven 1993; www.fda.gov.opacom/ethics 19/11/03).

( http://www.fda.gov/oc/ohrt/irbs/websites.html - 29/11/03)

US Independent Regulatory Body regulations (1982) provided the framework for the establishment of what we now call Ethics Committees, the primary function of which is to ensure safety of human study participants. To this end, the informed consent process remains a significant focus of their attention. At present, approval of an accredited and adequately constituted ethics committee is mandatory before a clinical trial may be started (Dept. of Health, 2000; MRC, 1998; WHO, 2000; www.ich.org/ich8.html - 20/11/03; http://www.fda.gov/oc/ohrt/irbs/websites.html - 29/11/03).

Further development in GCP has also come in the UK from the pharmaceutical industry in the form of the American British Pharmaceutical Industry (ABPI) Guidelines (1986), with similar developments in France with the Bonne Praciques Cliniques (1987). Similarly, in the United States, parallel developments came in the form of the Investigational New Drug (IND) Rewrite, of which the most notable contribution included guidelines around the reporting of serious adverse events. These guidelines not only ensure safety monitoring for patients, but also establish a basis for monitoring all adverse events throughout the drug development pipeline. Today, strict guidelines exist and are followed and the fatal serious adverse events even lead to stopping of some clinical trials especially if there is a trend that shows death to be related to the drug under study.

In 1988 the United States established the Monitoring Guidelines. These clearly stated the procedures to be followed for monitoring the conduct of clinical trials. Nordic Guidelines and Japanese Guidelines supported this. In France, Huriet Law was passed in 1990 (Raven, 1993; WHO, 2000; www.fda.gov.opacom/ethics -17/11/03).

In 1991 European Guidelines were implemented. In 1992 Australia joined and laid down the Australian Guidelines on GCP. It is also at this point that the World Health Organisation (WHO) developed Draft Guidelines. The eventual drafting of WHO

guidelines included recommendations that all states should adopt their own regulatory framework for GCP, based on the above. These were going to be in line with international GCP yet embracing the country specific requirements (www.ich.org/ich8.html - 22/11/03;

http://www.fda.gov/oc/gcp/default.html - 29/11/03).

The rapid development of guidelines across the world eventually led to the development in 1996/7 of the International Conference on Harmonisation (ICH) GCP Guidelines, which remain the world standard today. The International World Assembly on GCP Guidelines (Cape Town, South Africa, 1997), ratified and published the ICH-GCP Guidelines. These guidelines clearly stated what the sponsor's, ethics committee's, investigator's and the monitor's responsibilities (clinical researchers) are, in the conduct of clinical trials (www.fda.gov/oc/gcp/guidance.html - 21/11/03;

http://www.fda.gov/ohrms/dockets/98fr.html - 29/11/03).

### 3.3 The South African Guidelines

The South African Department of Health serves as the oversight for the Health Regulatory Authorities Medicines Control Council, which produced its first published guidelines on the conduct of clinical trials in 2000 (Department of Health, 2000). Clinical trials in South Africa have a long history based on South Africa's favorable

environment, with reasons of its technological and well-developed medical infrastructure and expertise.

In addition, the racial diversity provides an additional advantage for studies in which racial differences in treatment response might be anticipated (Department of Health, 2000). In the past, many studies focused on diseases believed to be associated with more rural populations, but with increased urbanization this approach has changed with the added advantage being that patients in urban settings are more accessible (Manyike, 2003).

In South Africa, clinical trials have been conducted in which evidence of poor study management and monitoring has been uncovered like protocol deviation specifically, exploitation of the poor, unethical and unnecessary conduct of clinical trials (Mnet, 2001). Furthermore, the rapid rate of growth in the number of clinical trials conducted in South Africa has further motivated government to regulate the research industry in the interests of patient safety. Particular concerns have been raised around the low levels of participant literacy and the vulnerability to exploitation that this ushers in (Department of Health, 2000).

### 3.3.1 The Rationale for the Development of South African Guidelines

The South African Guidelines were first published in draft form in September 2000, and now form a working document accessible on the internet (www.south African department health.ac.za – 12/23/03).

As a public document, interested and involved parties in the area of clinical trials are encouraged to refer to the document for current comprehensive GCP guidelines. This process is designed to ensure quality of the data generated in South Africa, whilst at the same time giving assurance to the public that the rights, safety and integrity of human subjects is maintained. This is inline with the 1996, ICH GCP guidelines.



### 3.3.2 History of South African Guidelines

In 1997, the World Health Organisation (WHO) developed the GCP Guidelines that defined the sponsor obligations and the investigator responsibilities. These guidelines were not designed to be exhaustive for all countries, but a basis form which individual countries could develop their own set of guidelines. These should in turn be relevant and in compliance with health authority regulations and government policy within independent states (Heilman, 1995).

These guidelines were compiled under the direction of the Director-General of the Department of Health in South Africa. Parties

involved in drafting the South African guidelines beginning in 1998 included: the Medical Research Council (MRC); Medicines Control Council (MCC); Universities of Natal, Witwatersrand, Medical University of South Africa (MEDUNSA), Cape Town (UCT), Free State, Rand Afrikaans (RAU) & Pretoria; Health Systems Research Directorate; Research Co-ordination Epidemiology and Directorate; Pharmaceutical Services; South African Institute of Medical Research; South African Pharmaceutical Clinical Research Association (SAPCRA); Health Professions Council of South Africa (HPCSA); WHO Collaborating Centre for Drug Policy; Lawyers of Human Rights (Department of Health, 2000).

### 3.4 Stages of Drug Development

Drug development is a long process that may take up to 15 years and is estimated to cost up to 15 US Dollars (Raven, 1993). Clinical trials form an essential cog in the drug development wheel in that they represent a gold-standard mechanism for generating independently examinable data from which pharmaceutical companies make applications for registration. Studies may be conducted after initial drug registration, but serve largely to establish the relative efficacy of registered compounds and may, in some cases, be used to seek registration for indications other than the primary one for which the drug was originally registered.

### 3.4.1 Pre-clinical Phase

This initial phase in drug development uses experimental animals to establish proof of hypothesis using best available animal models. In addition this phase examines toxicity and adverse effects including teratogenic potential (Heilman, 1995; MRC, 1998; Raven, 1993). Pharmaco-kinetic studies, which incorporate measures of absorption, also form part of this phase (MRC, 1998; Heilman, 1995; Raven, 1993).

### 3.4.2 Clinical Phase

This stage begins to incorporate human subjects in clinical trials. As with all clinical trials, safety of study participants remains the primary concern of study physicians and not the primary study objective (Dept. of Health, 2000; World Health Organisation (WHO), 2000; Medical Research Council (MRC), 1998). The clinical stage of drug development is divided in four phases as follows:

#### 3.4.2.1 Phase 1

This is the first phase of drug tests on human subjects and only incorporates healthy volunteers. The purpose of this phase is to establish the optimal dosing to optimize tolerability and includes only small numbers of subjects ($_{+/-}$ 10). These preliminary studies are usually conducted in hospital or commercial pharmacology units with specialists, to ensure safety through close observation. The standard

approach is to start with a single dose that is then increased based on tolerability. Study volunteers are paid for participating in the study. Phase I studies are infrequently conducted in South Africa few pharmaceutical companies have drug development centres in this country. Frequently volunteers include the medical / nursing students and employees from within the pharmaceutical industry (MRC, 1998; Heilman, 1995; Raven, 1993).

#### 3.4.2.2 Phase II

Phase II studies begin the process of drug investigation within the proposed target (sick) population. Again, numbers remain small and very close attention is given to issues of safety and tolerability. Only once this has been shown, may companies proceed to the third phase of clinical drug development in which a placebo arm is introduced in phase III (MRC, 1998; Heilman, 1995; Raven, 1993).

#### 3.4.2.3 Phase III

Phase III studies include much larger study (sick) populations and primarily seek to establish clinical efficacy. Safety data generated in this phase, however remains crucial and forms an important part of the final safety recommendations from the company (Department of Health, 2000; MRC, 1998). These studies are ideally multi-centre, and invariably, though not universally, multinational. Data from these

studies can then be used for worldwide registration and makes the need for harmonization of the essence of GCP guidelines clear.

#### 3.4.2.4 Phase IV

The final (post -marketing) phase of drug development that occurs after registration may serve a variety of purposes including dose modifications, new indications and relative efficacy to other treatments available for the same indication. This phase may also serve to identify rare adverse events (Dept. of Health, 2000; MRC, 1998; Heilman, 1995; Raven, 1993).

### 3.4.3 Other Access to Unregistered Drugs

Apart from the previously discussed phases, mechanisms exist through which drugs may be made available to patients on a named basis for a specific indication. These include the following situations:-

#### 3.4.3.1 "Named Patient" Drugs

In some circumstances one finds that there are drugs that can be used by certain patients because they benefit from those drugs. These drugs are unregistered but the application is made specifically for the "named patients" who are benefiting from that particular drug and where there is no alternative drug that can be used. Before supply of these drugs is allowed, permission should be sought from the regulatory authorities (Department of Health, 2000).

The application should be done by the specific doctor who has been taking care of patients whilst in the study, and who will continue taking care of such patients. This is done in consultation with the pharmaceutical company that has been conducting the clinical trial (see annexure 13). The clinical investigator is obliged to get consent from the patients before applying for permission to use the unregistered drug. Close observation is done so as to identify and report the serious adverse events. This is most frequently found in some of drugs used in HIV and cancer clinical trials (Dept. of Health, 2000; MRC, 1998; Drug Act 101, 1965).

#### 3.4.3.2 Expanded Access Scheme (Programme)

This scheme is found between phase III and phase IV. This may come to pass when a clinical trial is halted for a particular reason, but some patients on the study for whom the study drug is effective, may have access to continued treatment. Patients would have consented to participation in the original study and clause therein must have provided for continuation of the study drug until registration and availability commercially. At the same time the pharmaceutical industry would make a commitment to continue supplying the drug until registration or until the drug is commercially available (Department of Health, 2000; MRC, 1998; Heilman, 1995).

### 3.5 Principles of ICH GCP

The principles of GCP form the bases for conduct of clinical trials worldwide. Thirteen major principles cover all aspects essential to the conduct of a clinical trial (see annexure 14).

### 3.6 Principles of GCP: A South African Perspective

The South African guidelines begin by explaining the requirements and procedures to be followed when making an application to conduct a clinical trial in South Africa (see annexure10). These spell out in detail the requirements of sponsors, ethics committees, investigators and clinical trial monitors. Throughout, the focus is on the protection of study participants as well as quality assurance. Specific attention is given to the Ethical considerations for HIV/AIDS Clinical and Epidemiological Research (Department of Health, 2000).

The SA Guidelines have incorporated the strengths of numerous preceding documents from around the world. These include the following: Declaration of Helsinki (2000), International Guidelines for Ethical Review of Epidemiological Studies (1991), Council for International Organisations of Medical Sciences (CIOMS), ICH Guidelines for GCP (1996), ICH Harmonised Tripartite Guidelines (1997), Association of the British Pharmaceutical Industry Clinical Trial Compensation Guidelines (1991, 1994), World Health

Organisation (2000), WHO Technical Report Series. No. 850, Guidelines for GCP for Clinical trials on Pharmaceutical Products, (1995), WHO Operational Guidelines for Ethics Committees that review Biomedical Research, Geneva TDR/PRD/Ethics/2000.1 (2000), Institutional Review Board (IRB) Guidebook, Office for the Protection from Research Risks- National Institute of Health, USA (1993) and MEDSAFE, New Zealand Regulatory Guidelines for medicines, Volume3: Interim Good Clinical Research Practice Guidelines (1998).

Compliance with the SA Guidelines is mandatory in terms of the regulations over which the Director General of Health presides. Standardised application forms are issued and form the basis for standardised screening and evaluation of proposed clinical trials by the Medicines Control Council (MCC) of South Africa (Annexure 6).

The most critical areas of this application include:-

- A study protocol, which incorporates a clear study rationale and motivation. This area should in turn justify the study priority, country specific research questions and how they impact the local and regional populations, and finally how the results could potentially contribute to the improved health of South Africans.
- The study design, which should optimize the chance of being able to clearly answer the study question. This section should include

details of the proposed study population, the proposed sample size with adequate justification. If research is to include vulnerable groups (females, minors, mentally - ill, prisoners and similar groups) particular attention to be paid to the merit of the social and scientific aspects of the study. Indeed there are some who view study populations within a developing country such as South Africa as vulnerable by virtue of their limited access to modern treatments (Department of Health, 2000).

- Investigator competence: technical competence is assessed by education, knowledge, certification and experience. Particular to the South African guidelines is that the principal investigator must always be based in South Africa (Department of Health, 2000).
- Balance of harm and benefit – an analysis in which the risks should not outnumber the benefits. Special attention should be given to the participants with chronic life- threatening conditions. The high prevalence of HIV in South Africa impacts on most medical treatment settings and in this clinical area, raises particular questions around the question of availability of drugs following completion of the clinical trial.
- Transparency: Once research approval is obtained, regular reports should be submitted to the MCC, which sorts these into a central register. Such reports include information on the basic research question, the principal investigator, trial sites, date of approval, start/stop dates, summary report on study progress and the outcome. All funding provided by sponsor for various aspects of

the study should be declared. This information is captured on a central MCC database to facilitate co-ordination and systematic review of ongoing clinical trials and helps prevent unnecessary duplication of trials.

- Confidentiality**:** study subjects' rights to privacy should be ensured and maintained at all times in both paper and electronic study records that do not form part of the treating physician's process notes. With the high rates of illiteracy, the potential for violation in this and other areas is higher and needs careful control.

- Ethics Review: all clinical trials require independent ethics approval before commencement of any study related procedures. The composition of the Ethics committees is legislated and includes representatives from legal, scientific, non-scientific and lay backgrounds. The cultural diversity of many study populations in South Africa, make adequate representation sometimes difficult to achieve. Based on the progress and conduct of the clinical trial, the ethics committee has the power to recommend premature termination of the clinical trial on ethical grounds.

- Informed consent: The patient information leaflet should be should be written in accessible language to the layperson. This implies availability in the mother tongue of the participant and should be culturally acceptable. Undue influences and coercion should be avoided and the leaflet should state that a subject's premature withdrawal should not affect the availability of

alternative or future treatment. This consent may in most cases be sought by the investigator or designated person, however, a number of South African committees insist on this role being the soul duty of the investigator/ trialist.

- Safety monitoring**:** This is an ethical responsibility throughout the conduct of the study. Proper management and reporting of SAEs should be done at all times. This is in line with ICH GCP but the difference in South Africa is on the Regulatory progress reporting procedures and frequency (see annexure 12).
- Multi - centre studies: Here the focus is on the standardisaton of study procedures and record keeping across sites (local and international). When South Africa is chosen for a clinical trial and the study is not being undertaken in the country of origin, a full explanation should be given in support of this approach.

### 3.7 Responsibilities required by GCP

GCP is the cornerstone on which conditions conducive to the conduct of credible clinical trials are based. Guidelines seek to preserve the safety, rights and integrity of all study participants. It provides a clear framework for quality assurance through monitoring the standards of care of trial subjects, an important aspect of which is the informed consent process.

#### 3.7.1 The Independent Ethics Committee (IEC) Responsibilities

The main function of the Ethics Committee is to safeguard the rights, safety and well being of the subjects. The Ethics Committees are there as advocates for the patients. Specific responsibilities are as follows:

**Review of Clinical Trial Proposals:**

- To review the proposed clinical trial within a reasonable time and document recommendations/modifications required or approval following the committees joint decision on the review. There are studies that are seasonal thus should be evaluated with that priority in mind to ensure recruitment timeframes. Presently, South Africa is in the process of developing a National Ethics Committee (Department of Health, 2000; ICH GCP Guidelines, 1996).

**Documents for Review:**

The local Ethics Committee should receive and review a study protocol, investigational product brochure, patient information and informed consent documents as well as Curriculum Vitae (CV) of all staff that will be involved in the conduct of the clinical trial. They should consider the qualifications of the investigator before approval of the clinical trial.

**Approval of proposed Clinical Trial:**

- The approval should be specific, indicating the protocol number, sites and investigators to be involved in a proposed clinical trial. The review committee members should be known to the investigators. In situations when the investigator is a member of the ethics committee, he can attend the meeting but is not allowed to vote. The approval should specifically state that the particular investigator did not vote.
- The approval should specify that the investigator should report any deviation from the protocol and the reason for such deviations, and report any SAEs and new information that may adversely affect the safety of the subject.

**Composition & Functioning of the Ethics Committee:**

- Ethics Committees are composed of both scientific and lay people and should have at least five members. Members should be independent of the investigator or sponsor of the trial and only those that are independent of the clinical trial are permitted to vote or voice and opinion on the study under review.
- Ethics Committees should function in accordance with published standard operating procedures (SOPs) that are in line with GCP guidelines. Ethics Committee should make decisions at scheduled meetings at which a quorum must be present.

- Only members who participated in the review should be allowed to make decisions or vote.
- The ethics committee is at liberty to co-opt non-member experts in a particular area if deemed necessary.
- Ethics Committees should have all procedures documented, including the frequency of meetings and any need for expediting some reviews. All relevant documents like written procedures, membership lists, affiliation of its members and so on should be retained, as these may be asked for, by sponsors and investigators (Department of Health, 2000; ICH GCP, 1996).

**Patient Safety:**

- The committee should conduct ongoing review of the conduct of the trial to ensure patient safety. Progress reports should be submitted twice annually. All SAEs are reported to both Regulatory and Ethics committees as part of standard guidelines. .
- When a non-therapeutic trial is conducted, and the subject's legal representative is involved, the Independent Ethics Committee (IEC) should ensure availability of additional information, to protect the subjects.
- It should be ensured that informed consent is obtained prior to any study and that the questions pertaining to the protocol are answered before any subject gives consent to the study.

- The informed consent should be comprehensive, in layman's language, in the first language of the participant, and should meet the criteria of the standard informed consent established in all GCP standard guidelines. In some cases a guardian or a legal representative of a prospective participant may bewailed to be one of the consenting parties. Where the legal representative's consent is not necessarily required by the protocol, the IEC should ensure that the ethical concerns are met and that regulatory authority requirements are complied with.
- In South Africa the Amalgamated British Pharmaceutical Industry (ABPI) statement, is a mandatory part of the informed consent document. This is particularly important in settings that will include vulnerable communities that require specific protection from injury and exploitation (Department of Health, 2000).

The level and method of payment to subjects (if any) to avoid coercion and abuse, should be reviewed. It should clearly state that the subject should not incur any direct costs to be involved in the study.

### 3.7.2 Investigator Responsibility

**Competency & Qualification:**

- The investigator must be qualified in respect of education, specific study related training and experience to assume the responsibility of conducting a clinical trial. These details should

be contained in the individual investigator CV and submitted to the ethics committee for approval (Dept of Health, 2000; ICH GCP, 1996).

**Knowledge of the Protocol & Investigational Product:**

- The investigator should be thoroughly familiar with the use of the investigational product as described in the Investigational Drug Brochure (IDB) or protocol. Having this information will ensure that the investigator is able to intervene incase of drug reactions. And provide assurance that drug administration and dose modifications will be done correctly.
- The investigator should comply with the protocol at all times. He / she should not make any deviations without prior authorization from the sponsor and IEC, and deviations should be documented. A deviation may be implemented if this will prevent an immediate hazard to the subject, but should be immediately reported to the sponsor, regulatory authority and IEC.

- Investigational Drug: The investigator remains accountable for the investigational product even when the pharmacist or other staff member has been delegated to manage this aspect. Safe and correct storage of the study drug is required, thus ensuring that study drug is used only for clinical trial purposes, and that he or a delegated person explains the use of the study drug to the patient. Drugs should be

stored in a lockable area with controlled access to ensure safety of subjects and study drug.

- Patient treatment allocation: The investigator is responsible for randomisation procedures as well as unblinding protocols in accordance with GCP and the study protocol. The specific circumstances of r unblinding will usually be study specific.

- Study types include:-

  - Open label studies: in which the investigator prescribes a known drug to a patient and the outcome is tested.

  - Single blind studies: In this case, the investigator is aware of the treatment status of the participant, but the later remains blinded. An example may be that a diagnosis is made. e.g. injecting the fluorescent fluid (drug) versus placebo (normal saline) to identify or diagnose the abnormal growth in the patient's body. Injection of both the drug and placebo would look alike but the actual final and necessary outcome will differ when the special post-test or x-ray is done.

  - Double blind studies: In this case, both the investigator and the patient do not know whether a subject is receiving active treatment/s or placebo/comparator.

Randomisation information is available onsite in case of emergency unblinding (for example an SAE) where knowledge of the treatment allocation will affect immediate treatment. Specific guidelines of when and how to break code are defined in the protocol. In all cases the sponsor should be notified of such action. In some instances, the group responsible for the randomization schedule may need to be informed before the code is broken. This may lead to the patient being withdrawn from the study.

- Double dummy studies: Where certain study sites are not provided with any active study drug. This is uncommon.

**Obtaining Informed Consent:**

- Informed Consent: Written informed consent is obtained prior any study procedure and should involve no coercion, should ideally be in the subjects home language (challenging in the South African context with 11 official languages) and should not infringe on a participants rights to present or future treatment. The methods used in obtaining informed consent should be culturally acceptable (Dept. of Health, 2000; ICH GCP, 1996 ).
- The subject or legal representative should be given adequate time to make a decision on whether or not to participate in the clinical trial. If the subject and his legal representative are unable to read

and write, an impartial person should be present during the entire informed consent procedure (Dept. of Health, 2000; ICH GCP, 1996).

**GCP Knowledge & Compliance:**

- The investigator should be aware and comply with the GCP requirements. The investigator should undergo CGP training in order to equip him/herself with knowledge on the conduct of clinical trials. He /she should permit monitoring and auditing by the sponsor, as well as inspection by the regulatory authority. The investigator should allocate time to spend with the monitor so as to discuss the problems encountered at the site. The investigators (Principal and sub-investigators) sign a Declaration of Intent (refer annexures 7 and 9), in which a commitment is made to abide with the ICH GCP guidelines throughout the conduct of clinical trials (Dept. of Health, 2000; ICH GCP, 1996).

**Ensure Site Capacity**:

- There should be a list of people to which specific study related duties are delegated. This ensures that each trialist does what is within his/her scope of practice. If a new member joins the team during the study she/he is first required to sign the duty delegation form before participation in the study may commence, assuming

that regulatory authority and ethics committee approval has been granted (Annexure, 6; Dept. of Health, 2000; ICH GCP, 1996).

- The study site should have the appropriate infrastructure to properly conduct clinical trials, and includes physical resources, staff and time. For this reason the MCC is concerned with the study load of each participating site. This promotes both patient safety and ensures proper handling of data to ensure credible results (Dept. of Health, 2000; ICH GCP, 1996).

- The investigator should ensure that the staff members are adequately trained and understand the protocol. Regular protocol discussions will ensure that the research staff is kept up to date. The protocol should be strictly adhered to throughout the clinical trials, deviations from which or non-compliance with, may lead to adverse outcomes and unreliable data, potentially endangering patients (Dept. of Health, 2000; MRC, 1998; ICH GCP, 1996; Raven, 1993).

- Ensure that medical care of patients is given by medically qualified person (doctor). This is the reason why it is emphasised that apart from doing research, the clinical investigators should know that they have a duty to care for the patients. This is part of the provisions of the Declaration of Helsinki (2000).

**Communication with the Subject's Primary Physician:**

- The clinical investigator should inform the subject's primary physician of his/her patient's participation in a clinical trial if consented to by the subject. This ensures continuity of care during and after study completion. This is more important in situations where study drugs could adversely interact with other medications. Some patients need a "washout period" before other drugs are given. The clinical trial participant needs to be educated on such issues, so that should it happen that he/she gets sick, he/she notifies the relevant physician of his/her participation in a clinical trial (Department of Health, 2000; ICH GCP, 1996).

**Premature Withdrawal of Subject:**

- Subjects' withdrawal from a clinical trial may be for any number of reasons. Some of the reasons include investigator decision, side effects (drug allergy, toxicity) or lack of efficacy, worsening of the clinical condition or indeed patient's withdrawal of consent. It is the trialist's duty to establish the reason for withdrawal of consent but the patient should not be coerced to continue with the study, since this will be violation of human rights (Department of Health, 2000). Withdrawal from the study should not affect the patient's treatment at the same institution, instead the trialist should advise the patient on available alternative treatment. The subject is not obliged to provide reasons for consent withdrawal.

(Dept. of Health, 2000; MRC, 1998; ICH GCP, 1996; Raven, 1993).

**Premature Termination of the Clinical Trial**:

- Premature termination of the study: it is vital to inform the subjects if the clinical trial is prematurely terminated. If this is decision is made without the knowledge of the sponsor, a detailed explanation should be given to sponsor and IEC. If the sponsor suspends or terminates the study, the investigator should inform the institution and IEC. (Dept. of Health, 2000; MRC, 1998; ICH GCP, 1996; Raven, 1993).

**Specific Duties:**

- Application to Regulatory Authority: The application to the regulatory authority becomes the investigators responsibility if the study is investigator driven and when the study drug is going to be used for specifically named patients. Otherwise this is the Sponsors responsibility. Standard forms are available for this process (See Annexure 6). This form covers the objectives of the study, the rationale and justification as to why is it important that the study be carried out in South Africa. It becomes more critical if the study is carried out in South Africa and not the country in which the pharmaceutical company is based. In the light of past exploitation, the Health Department is particularly vigilant

regarding the use of the South African population for phase I and II studies (Department of Health, 2000; Morse, Simon, Resch & Walker, 1995).

- Application to Ethics Committee: This function is the responsibility of the investigator, though frequently the sponsor may be involved in assisting with this process. No trial related procedures may be undertaken without approval of the appropriate ethics committee. The ethics committee should be provided with all trial related documents for review. Some requirements may vary between committees.

- Study Progress: Regular study progress reports should be submitted to regulatory, ethics committees and in practice also the sponsor. (See annexure 12)

- Data handling and record keeping: The investigator should maintain all study documents as required by local regulatory authority, sponsor and GCP throughout and following closure of the study. The clinical investigator has a duty to keep accurate, complete and clean (define in this context) records including Case Report Forms (CRFs) for possible future scrutiny. Data reported in CRFs should be consistent with source documents and any discrepancy should be explained. Errors should be corrected by drawing a line to cancel, but not obscure the incorrect entry, after which the correct entry can be made and should be accompanied by a signature and date. In some instances, one is expected to give the reason for changing the data that has been previously entered.

Sponsors vary in their requirements in this area and should provide investigators with details on this issue. Every trialist should undergo training in data handling and corrective measures to be used, in order to comply with GCP requirements.

- Patient safety: The investigator should provide progress reports to IEC and the sponsor as per requirements. Furthermore, all SAEs should be reported immediately to the sponsor and the IEC/regulatory authority. All adverse events (AEs) should be documented. In case of death during the clinical trial, the report from the autopsy should be given to the sponsor.

**Agreements:**



The investigator enters into a series of agreements with the sponsor including confidentiality, protocol adherence, financial disclosures and other sponsor specific agreements.

The investigator should have all financial aspects of the trial documented in an agreement document that is signed and witnessed by all involved parties.

### 3.7.3 Sponsor

The sponsor carries ultimate responsibility for the conduct of the clinical trial. Specific area of responsibility include the selection of investigators, the application to regulatory authorities to conduct the

trial, study initiation, quality assurance, study termination and finally publication of results.

In some instances the sponsor may elect to outsource some or all trial-related responsibilities to Clinical Research Organisations (CRO), but even so, final responsibility remains that of the pharmaceutical company.

Sponsor appointed monitors or Clinical Research Associates (CRA) are tasked with the responsibility of ensuring that the study is conducted in compliance with the approved protocol. In summary the sponsor responsibilities include the following:-

- Quality assurance and quality control: the sponsor should ensure that the SOPs and GCP guidelines are adhered to. This is applicable to all stages of the trial.
- Trial management, data handling and record keeping: the CRAs supervise this aspect as per protocol and regulatory requirements. Allocation of responsibilities should be done prior to the start of the study and should ensure maintenance of a security system to avoid unauthorised access to the study documents.
- Compensation of subjects: the regulatory authority and IEC requirements state that the sponsor should have insurance and compensate the participants for study related injuries.

- Financing for the investigator and participants (if any): this should be documented in a form of an agreement. This is a legal document that binds both parties involved and should be declared in full to regulatory authorities and ethics committees.
- Submission for approval: to the regulatory authority for permission to conduct the clinical trial prior to the start of the study. Confirmation of IEC approval from the investigator or institution is required to supplement this approval.
- Provision of Investigational Drug Brochure (IDB) or package insert to the investigator and regulatory authority: This ensures that the investigator will be equipped with all the knowledge about the drug before and during the study. Updated information for the study brochure should be distributed to all trialists involved with the study as well as ethics and Regulatory authorities.
- Manufacturing, packaging, labeling and coding of investigational product – labeling of the study drug should clearly indicate that it is for clinical trial use only; expiry or retest dates should be clearly stated as well as the conditions / temperature under which the drug should be stored. The sponsor is responsible for the supply of the study drug to the investigator site, which may only happens once Regulatory Authority and IEC approval is finalised.
- The study agreement with the investigator should contain a clause in which the sponsor, IEC and regulatory authority are given

access to records and essential documents, should this be deemed necessary.

- Regular safety evaluation of investigational products and reports should be given to the regulatory authority. Sponsor and CRA should expedite reporting of SAE to regulatory authorities and ensure regular updates.

### 3.7.4 CRA responsibilities

Monitors form a link between the investigator, sponsor and regulatory authorities. Their duties include the following:

- Monitoring of the conduct of the study. This implies that they are appropriately trained, and possess the requisite scientific or clinical knowledge to monitor the trial adequately.
- To act as the main line of communication between the sponsor and the investigator. To verify that the investigator has adequate qualifications and resources. If there is any identified lack of trial related knowledge, the monitor should support the site by educating the staff to bridge this gap. The monitor should be available at all times for the site to address any queries and uncertainties.

- Investigational Product: CRA should verify that the investigational product storage conditions are acceptable and that the supply is

adequate throughout the trial. The clinical supplies should be in lockable cupboards. He / She should verify the correct usage, including drug dispensing and patient compliance.

- Source Data Verification (SDV): CRA should verify that the investigator follows the approved protocol and all amendments. This is done during monitoring visits. This process also checks informed consent procedures are adequately followed and verifies the existence of trial patients. It is also essential to ensure and verify that the written informed consent was obtained before the subject's participation in the trial for an example before any study–related procedure was executed.

    - The monitor should verify that the investigator is enrolling only eligible patients by verifying inclusion and exclusion criteria are complied with and that these are consistent with source data.

    - He / She should verify that the investigator has all application documents , reports and submissions completed timeously. These should be correctly dated and identify the specific trial. The protocol number, title and reference number are used to identify the study. He / she should verify that all source documents and trial records are accurate, complete and up to date. Checking for completeness should include checking that information specifically required by the protocol is also recorded in the CRF and source documents.

    - Reporting of Adverse Events (AE) and Serious Adverse Events (SAE): The monitor should ensure that the AEs and SAEs are

timeously recorded together with concomitant medications and illnesses.

- He / she should verify that the investigator provides written reports with reasons of all dropouts and premature withdrawals in the CRFs.
- The monitor should inform the investigator of any discrepancies between source notes and the CRF data and ensure that the appropriate corrections, additions or deletions are made, dated, explained (if necessary) and initialed by the investigator or delegated staff.
- Monitors should communicate deviations from the protocol to the investigator, taking appropriate action designed to prevent recurrence. If necessary, further training should be carried out.
- Monitors should ensure that the monitoring is carried out with strict adherence to the sponsor's SOP and submit comprehensive monitoring reports of all findings at site visits (ICH GCP, 1996).

### 3.8 The Informed Consent

This is a document signed by a subject in which he/she voluntarily confirms his or her willingness to participate in a particular trial. This is done after being fully informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and

dated informed consent form (Declaration of Helsinki, 2000; Department of Health, 2000; ICH GCP, 1996).

In situations where the prospective participant is unable to provide informed consent to participation in a research study (like minor children, as examples), the legal representative or parent/guardian should be approached to provide this consent. In addition, the child is also required to provide his/her assent to participation in the proposed clinical trial (Dept. of Health, 2000). Other special groups in respect of the consent process, for example those with mental incapacity, will also require the involvement of the guardian/primary caregiver. In this instance, particular attention should be given to this process and the ethical pitfalls that this may introduce. The importance of conducting such studies should be easily justifiable based on scientific merit in the particular patient population in a particular setting (Dept of Health, 2000). For those potential participants that are in prison, special steps need to be taken to get approval to conduct research as coercion may be difficult to avoid completely in such settings (Department of Health, 2000; MRC, 1998; Morse et. al. 1995).

### 3.8.1 Informed Consent and Previous Studies:

Patient information leaflet and consent documents have a number of items that are mandatory to include. In a study enquiring of clinical investigators what they would include in consent documents, 50% of respondents in Spanish hospitals, where the study was conducted, would not have included an invitation to prospective participants to participate in a particular study. When asked whether they would explain all known risks in participating in the study, 40% said no as they felt this may "scare" prospective participants away and increase rates of psychological adverse events as a result of sensitization (Komen, 1999; Dal-re, 1992).

Similarly, elements related to voluntariness of participation and experimental nature of the study, were also not priorities to the respondents in this study.

A number of studies in the US have been highlighted historically as having been performed without proper attention to matters of consent. For instance the Tuskegee Institute Studies in the 1930s (Sidley, 2001; Thomas & Quinn, 1991), in which African American participants neither consented to participation in the study or to having known effective treatment for syphilis withheld for up to four decades in some cases. This violation of human rights and other studies with improper conduct of a clinical trials as indicated in Swanson & Ward (1995) and Komen (1999), resulted unsurprisingly in significant resistance on the part of African Americans from future

participation in clinical trials

(www.journeytowellness.com/clinicaltrials2/html - 01/07/04).

### 3.9 Human Rights and Clinical Trials

Clinical trials are dependent on human subjects for their existence, however, this setting also provides rich pickings for compromised attention to human rights. Factors that increase this vulnerability include low levels of education, illiteracy, lack of transparency with regard to access of information. Advertisements and other recruitment efforts will seldom reach all the target population, and urban residents are more likely to reside closer to research settings (Manyike, 2003).

For clinical trials to be generalisable, it is important that the population recruited should be truly representative of the country population. Studies on Recruiting Ethically Diverse Research Participants and minority groups, reject the terms race and minority in favour of culture and ethnicity. They state that what is important in recruitment is recognition of culture as a specific system of shared beliefs, rules and values (Olin, Fox, Bower & Schneider 2002; Moore, 1997).

These aspects clearly have particular relevance in South Africa because of our considerable cultural and ethnic diversity, low literacy rates and so on. Plainly put, these and other factors translate to the fact the majority of the population remain the least exposed to and

represented in clinical trial populations in South Africa (Duant, 2003; Manyike, 2003; Haulman & Bomar, 1995). As part of the protection of human rights, the ethics committees place great emphasis on the fact that the informed consent should be correctly taken. In this regard, information should be accessible to the target population in respect of language and vocabulary (Duant, 2003; Manyike, 2003; South African Medical Association Research Ethics Committee, 2003; Haulman & Bomar, 1995; Department of Health, 2000).

Previous studies have indicated that the attitude towards recruitment for clinical trials for a diverse population is directly influenced by ethnicity, socio-economic status and the ability to speak English (Duant, 2003; Manyike, 2003). Furthermore, numerous studies contain imbalances in recruitment in these areas that have a potentially significant impact on the generalizability of study results as alluded to above (Welsh, Adam, Fontaine & Gjerdingen, 2002; Harris, Gorelick, Samuels & Bempong, 1996; Robertson-DeGennaro, 1994).

### 3.10 The South African Guidelines – country specific concerns

#### 3.10.1 Issues Related to HIV/AIDS Research

**Research should be appropriate for South Africa:**

For reasons previously discussed complemented by United Nations AIDS Initiative Support Organisation (UNAIDS), most of the South African population are regarded as vulnerable people. Some of the criteria on which this categorization is made include:-

- limited economic development
- inadequate protection of human rights
- discrimination on the bases of HIV antibody status
- inadequate community / cultural experience with scientific understanding of scientific research
- limited availability of health care and treatment options
- Inadequate provision of informed consent (Department of Health, 2000).

#### 3.10.2 HIV Related Drug Trials and Access to Medication

Clinical trials in the area of HIV are not exclusively focused on vaccine testing and immune system boosters, but on an array of treatments, which are emerging for the treatment of diseases that co-occur with HIV. In addition, presently available anti-retroviral drugs

are effective, but expensive and remain largely inaccessible to the public sector (Department of Health, 2000). As alluded to earlier, clinical trials provide many patients with a possibility of having a trial of therapy on expensive and inaccessible drugs. As a consequence of this situation, which makes exploitation a risk, the MCC highlights the importance of the researcher giving full information on the implications of participating in clinical trials and the advantages and disadvantages of having medication for a limited period, which is duration of the study period. Proposals that are unable to address and guard against the potential for abuse of vulnerable patient rights, will rightly be viewed with the necessary caution by the MCC review panels.

### 3.10.3 HIV Testing



The complexity of research trials in this area implies the potential for unforeseen consequences to trial participants, and these risks need to be weighed up against the potential benefit to a group of patients. A lot of support system and counseling is needed on this matter.

### 3.10.4 Side Effects

Antiretroviral regimes in use in South Africa in the public sector induce a range of undesirable adverse effects, which may in turn precipitate the premature withdrawal of a participant, with the potential for compromising study results. Informed consent documents in this important area of study, should include explanations as to what should be done; and reassure participants that

their right to treatment will not be compromised, nor their right to protection (Department of Health, 2000).

### 3.10.5 Research Standards

The South African community is characterized by sub-optimal living conditions and poor access to good social and health conditions. The MCC emphasizes on use of optimal quality and ethical standards in research for both vulnerable and non-vulnerable communities. Local and international standards should be the same. This is the reason compliance with the South African Guidelines are compulsory for all clinical trials done in South Africa (Department of Health, 2000).

### 3.10.6 Use of Placebo

Modern guidelines suggest that it is generally unethical to utilize placebo treatment in the context of effective and available alternative treatments. Occasionally, it may be acceptable to use a placebo arm in countries that do not have access to interventions that are the standard care in developed countries, however, this is a contentious issue.

### 3.10.7 Patient Management after Withdrawal from Clinical Trial

The patients should be advised about the post-trial management. The subjects that have shown a positive response to medication,

should continue getting the supply of medication, it is unfortunate that at this juncture the anti-retroviral drugs are not available to any extent, in the public health sector.

### 3.11 Issues Under Debate Between Pharmaceutical Companies and the Health Regulatory Authority in South Africa

Section 1.2 of the South African Guidelines state that "compliance with the South African Guidelines on conduct of clinical Trials is compulsory" (Department of Health, 2000). However some areas of dispute exist between the MCC and the pharmaceutical industry (Pharmaceutical Medical Association, 2000). Some of these include:-

- Provision of medication to the participants beyond end of the clinical trial - this is more particular in the HIV/ AIDS related studies.

- Commitment of the clinical investigator to take care of the subject or continue to monitor them beyond completion of the clinical trial.

- Use of placebo in clinical trials.

- Inclusion of advantages and disadvantages of HIV testing in the informed consent forms.

- Referral to an accessible centre for ongoing psychosocial support and basic medical care for those that are infected with HIV.
- Restrictions in the use of incentives in clinical trials.
- Rights to publication of results.
- Adoption of the year 2000 Declaration of Helsinki by South Africa yet other countries worldwide are still debating its content (Pharmaceutical Medical Association, 2000).

### 3.12 Clinical Researchers Training

Clinical researchers should receive training for each individual study in which they hope to participate. This requirement is satisfied through investigator meetings that precede study initiation. The study initiation meeting is primarily to train additional site staff that will be involved in the study, GCP training should now be mandatory for all study staff. Additional training may, if required, be offered by the study monitor and also continuous support and education, as the need arises during the progress of the study.

## 3.13 Previous Studies

Only a very small literature on the development of GCP training modules is available.

### 3.13.1 Previous GCP Audit Findings on Clinical Trials:

FDA audit findings most frequently include matters related to informed consent, failure to comply with inclusion/exclusion criteria , failure to perform protocol required tests, inadequate source notes and safeguarding of confidential documentation (Freedman, Simon & Faulkes, 1995 ).

The vigilance with which protocol is adhered to increased many fold following the publication of fraudulent study results in a prominent American journal in 1999. In this work conducted in a South African institution, for reasons of non-adherence to protocol, fewer than 30% of randomized subjects provided useful data on completion of the study. The result is that a number of vulnerable subjects were exposed to study medication, and possibly had standard treatment delayed for the duration of the study, all to no avail. In an ensuing investigation, it was discovered that nine other trials reported by the same scientist, were not as claimed in the publications, reviewed or approved by the appropriate institutional committees (Sidley, 2001; Gotlieb, 2000).

This degree of fraudulent conduct on the part of researchers, should attract the strongest possible action from regulatory and professional bodies. In the case of the scientist referred to above, he has been prevented from continuing his research career (Sidley, 2001; Gotlieb, 2000; Thomas & Quinn, 1999).

### 3.14 Instrument Development

Various instruments (symptoms scales) are used to collect data in a standardised way in clinical trials. These instruments can be used to acquire information on a wide range of subjects related to the patients wellbeing. Instruments are invariably developed with a specific patient population in mind, and are thus designed to "extract" the desired information (Tan,1992; Brink, 1989). The procedure to be followed when developing an instrument will be discussed in chapter four.

### 3.15 Needs Assessment

In assessing training needs, some authors suggest using a "what is versus what should" approach (Stufflebeam, 1971). Others (Mcniff, Lomax & Whitehead, 2000) suggest that the focus should be what can possibly be done to improve the situation, or is feasible for the situation, considering the environment and available resources (Reviere, Berkowitz, Carter & Ferguson, 1996; Laufer,1987; Madaus,

Scriven & Stuffebeam, 1987). In addition, principles of adult learning are underpinned by influential motivating factors that impact on the reasons for learning in the first place (McNiff, Lomax & Whitehead, 2000; Lauffer, 1987; Madaus, Scriven & Stuffebeam, 1987).

For an organisation to grow and maintain operational efficiency, programmes need to be developed and implemented to develop staff and dynamically alter company and business focus. Training programmes developed for these specific needs are potentially valuable tools with which to achieve this end (Grant & Davis, 1997; Walters, 1997; Jarvis, 1996; Knowles, 1984).

Planning, clearly a crucial element to this process may subscribe to a number of approaches. Knowles (1984) puts emphasis on the need to diagnose needs of adult learners prior to developing an educational strategy. Gillies (1994) refers to the same step as "situation analysis", a more generic term for a similar process. A different approach is the more active solicitation of learners' inputs to describe their own needs, thus encouraging participatory learning ( Beard & Hartley, 1984; Bloom, 1954). If nothing else, this approach is likely to ensure "buy-in" from trainees (Walters, 1997; Jarvis, 1995; Gibbs, 1988; Knowles, 1984).

In the context of training need assessment, some authors use the terms need and gap interchangeably either of which may be appropriate in a particular context (Staffelbeam,1971). Others, however, insist on the view that a need carries the denotation of discrepancy or gap between some desired, acceptable condition or state of affairs (Witkins, 1984). Another group of authors have been able to defend their understanding of need as the difference between 'what is and what should' (Madaus et.al, 1987). There are also those who take a dimensional approach to understanding need (Madaus et al., 1987) using democratic, diagnostic and analytical dimensions. A need is seen to be democratic in a sense that the majority of the reference group desires a change. It is diagnostic in a sense that its absence or deficiency can prove to be harmful to the existing or desired situation (Madaus et.al. (1987).

An analytic approach views need as a direction in which improvement can be predicted to occur given information about the current situation. The analytic view emphasises systematic problem solving and improvement. Madaus (1987) and Whitkins (1988), further classify needs assessment into two or more types depending on the purpose for classification. The preparatory type is seen when a product or program is being planned, whilst the retrospective one is when the product / program already exists or the program has been implemented (Des Marchais, Bureau, Dumais & Pigeon, 1992; Dewey, 1984).

### 3.15.1 Steps in Needs Assessment

Witkins, (1984) recommends that goals or philosophy should be given as a point of departure for the needs assessment. To this end, GCP guidelines give some indication as to what may or may not be discussed, and focus on correct conduct in clinical trials so as to ensure patient safety. Barriers and constraints are looked into so as to identify and prevent factors that will hinder the change process.

## 3.16 Principles of Adult Education

People who are involved in conducting clinical trials are adults, so the characteristics of adult learners are relevant.

- **Self-concept**

Knowles, (1984) puts emphasis on the fact that adult learners are more independent and self-directed (Jarvis, 1996).

- **Experience**

Experience grows with subject maturity and may render people more receptive to learning for which he/she is motivated, and ultimately become a reservoir (Kreber, 1998).

The majority of clinical researchers are professionals with trial related experience that brings exposure to situations and a variety of fields. In designing a model, cogniscence needs to be taken of the strength of experiential techniques including discussions and problem solving situations (Knowles, 1984). By implication, this approach may run into difficulty in the context of acquiring new knowledge.

- **Readiness to Learn**

As a person matures, his readiness to learn becomes oriented increasingly to the developmental tasks of his own social roles. Knowles, (1984) refers to teachable moments. He points out that the relevance of the subject matter or education becomes clear if it is needed to carry out a particular task. It is then important to deal with topics that are relevant to conducting clinical trials so that these carry weight and will be viewed as a dire need for every researcher to know. This will ensure that the knowledge acquired is ready for use in a specific situation (Knowles, 1984).

- **Orientation to Learning**

This is directly related to the previously discussed concept of readiness to learn. As a person matures, his time perspective changes from the one of postponed application to that of immediate application of knowledge. This approach moves the focus from of

subject-centeredness to that of problem-centeredness (Knowles, 1984).

Brookfield, (1986) places emphasis on the need for individuals to define their own needs and goals (Knowles, 1984). Both of the abovementioned authors build on the principle of positive self-esteem. Having this quality in an approach to learning, increases the value of the process in pursuit of these specialized goals. Both authors are consistent with a systems approach to training in that they acknowledge both sameness and differences of the sub-systems or units with the proviso that cohesiveness in pursuit of the common goal can be achieved as described by Gillies (1994).

- **Motivation to Learn**

As a person matures, one gets more motivated to learn and this is more of an internal feeling than an external one. When an adult needs to learn, he/she does not necessarily need to be followed or pushed but is internally motivated to achieve a self-directed result.

As a consequence, the adult teacher is able to use a range of principles and methods to achieve the training objective. These include active participation, problem-solving scenarios, use of audio-

visual materials, and discussion (McIntyre & Byrd, 2000; Walters, 1997; Jarvis, 1996).

Apart from this approach being applicable to a trainer and prospective GCP trainees, this process also has the advantage of equipping investigators as to how to deal with patients in general and impart information to those participating in clinical trials and in particular in the area of informed consent (Kusche, 1993).

### 3.17 Development of a Training Model

The development of a training model will necessarily be based on the principles outlined and discussed in Good Clinical Practice guidelines. As such, both international and local guidelines, the results of training needs assessment, recommendations from the experts, ethics and regulatory authorities, and finally input from specialists, statisticians and essential stakeholders will be incorporated into this process.

The Florida State University (FSU) College of Medicine recommended that most of the curriculum or training models should be: **Student-centered.**

The environment should be designed in such a way that it shows respect for students, while being supportive of the training needs of

students. The decision to explore student needs prior to development of a training model, is anticipated will contribute to the reliability of the model to indicate and achieve the desired behavior and outcomes that are required in training future participants

(http://www.med.fsu.edu/education/policies.asp.htlm -06/18/03).

### 3.17.1 The Characteristics of a Training Model

- The model should be contextualized within an educational plan: It should specify how a student can use and apply the acquired knowledge. Clinical presentations with simulated and real patients are a powerful tool that should be used to stimulate learning. These tools should include case-based learning sessions that not only stimulate learning but promote application of basic sciences (McIntyre & Byrd, 2000; http;//med.fsu.edu/education/policies.asp.htlm.-06/18/03).
- The model should incorporate measures of competence that include but are not limited to the following:
    - professional values, attitudes and behaviors
    - moral reasoning and ethical judgment
    - essential communication skills with patients, families and colleagues
    - application of basic biomedical and behavioral sciences to patient care

- essential clinical skills
- problem solving and critical thinking skills
- life-long learning and information management. It is important to have specific guidelines as to how frequently should one attend the course, including updates and refresher courses.
- Socio-cultural and community context of health, illness and care should be known by the clinical researchers that will be dealing with clinical trial participants, so as to ensure correct approach and safety of trial subjects.
- organizational control systems that support the model so as to ensure quality improvement.

- Stake-holders and organizations should encourage scholarships and give support in the discovery of the new knowledge that will facilitate quality conduct of clinical trials

Crossland (2001) puts emphasis on the role of the sponsoring pharmaceutical companies in ensuring compliance with GCP, through a robust audit system. The success of an audit process is based on adequate training of clinical investigators who are responsible for the site-based management of all trial-related activities (Crossland, 2001; http://www.acrpi.com/crf/12-5 crossland.html- 05/07/2003).

The model to be used should be comprehensive yet flexible, so as to allow different teaching approaches and teaching aids that include case studies, simulations, video and demonstrations of procedures in practical situations (McIntyre & Byrd, 2000; Walters, 1997; Longworth & Davies, 1996; Fuhrman & Malen, 1991).

The St. Vrain Valley School District Office of Professional Development (2003) recommends that training models should include the following features:

Be result-based with a clear set of standards, ongoing assessments and purposeful instruction. Such models are dependant on clearly defined outcomes. It is stated that continuous evaluation will be part of the process. The implementation (throughput/process) will include:-

- exploration of theory through lecture
- demonstration or modeling of skill
- practice of skill under simulated conditions
- follow-up through feedback about performance
- coaching in the workplace

The ideal model will then result in the best practice if:

-it is grounded in research-based content to support student and professional learning

-it is designed to match the development and learning needs of participants

-it is spaced in such a way that it allows theory and practice including coaching (St. Vrain Valley School District, 2003).

### 3.18 Knowledge, Attitude and Practice

Previous studies have indicated that there is a strong link between the knowledge levels, of a particular topic, therapeutic area and attitude towards the particular health therapeutic area and practice (Ausubel, 1967; Batty, Jette, Bacon et. al., 1971). The more health professionals know about a certain therapeutic area or topic, the more comfortable they are with the use of relevant clinical practice and the more positive their attitudes are with that therapeutic area, which has as a consequence increased competence and standard of care. This has been observed for example in an immunization health education program in China (Zhang, Wang, Zhu & Wang, 1999) showing utilisation and distribution of staff in a nursing model (Stone & Tourangeau, 2003)

Similarly, if investigators are more knowledgeable and experienced in GCP, there will be a more positive attitude and compliance with the practice.

### 3.19 Conclusion

This chapter has dealt with literature that forms the basis on which the present study is based. This has included a review of Good Clinical Practice (local and international), it's history, development and how it influences the conduct of clinical trials worldwide. Previous GCP related audit findings in have informed in part the direction the researcher will take in this work. The review then focused on instrument development; training needs assessment; adult education requirements and development of a GCP training model, after which the research design can now be described.

# CHAPTER 4

# RESEARCH DESIGN

## 4.1 Introduction

The research design covers the three objectives of the study and incorporates the theoretical framework of the modified systems theory discussed in chapter two.

## 4.2 Rationale For Using The Study Design

A survey of training needs cannot be done without developing an appropriate instrument first, since there is no existing instrument.

The same applies to the third objective, of developing a training model. This final phase, which is development of a training model, cannot take place without being preceded by a training needs survey. The surveyed needs, form the basis of the content of a training model. With the use of a systems approach, the smooth flow of these interrelated phases of the study are ensured.

## 4.3 The Research Design

An empirical approach with a survey as the primary investigative tool permits testing specific deficits in knowledge in

this area to achieve the initial study aim (Munro, 1997). The use of key informants will form an important addition to enhancing the eventual details of the survey. The researcher will then utilise the survey results to develop the anticipated GCP training model in the final stage of the study.

### 4.3.1 Validity and Reliability:

Validity and reliability is ensured throughout the conduct of the study. This is taken care of by following the scientific approach as per protocol proposal. All stages in the study are followed as described in the research methodology study. The deviations are documented and limitations are acknowledged and documented. Gabs are acknowledged as areas that could not be covered are highlighted and documented as recommendations for future research.

In instrument design validity is established by following the criteria for instrument development (Foddy, 1994). These criteria are well described in the literature and cover all aspects of GCP while including anticipated gaps in knowledge demonstrated in previous studies and audit findings (Franzen, 1989).

Content validity will be ensured to ensure that it covers all areas of content derived from the literature, web search and key informants' recommendations. Construct validity is ensured by adhering to the

principles and guidelines in respect of instrument development (Mastaglia, Toye & Christjanson, 2003; Edwards & Talbert, 1999; Eitington, 1989).

The initial checklist is used to ensure that all intended areas and points are covered and face validity is established when the instrument has been designed, and given to experts for evaluation and recommendations (Dweyer, 2001; Foddy, 1994).

Reliability of the instrument will be ensured by the test retest approach. The instrument should cover all the elements set out in the study objectives. (See sections of annexure 4), while being designed to reliably yield the same information if used in future. The final re-test phase of instrument validation is beyond the scope of the present study.

### 4.3.2 Ethical Aspect of the Study

The ethical aspect will be observed at all stages of the study, starting from instrument development, conducting a survey for training needs up to designing a training model (McAlpine, Kristjanson & Poroch, 1997).

Before the beginning of the study, permission was obtained from the University Ethics Committee (see approval document which is annexure 2).

The key informants gave verbal consent whilst the survey participants, had letters attached to their questionnaire. See annexure 1.

In instrument design, the respondents like key informants, were informed that their participation was voluntary and confidentiality safeguarded. In case there is information with reserved rights, written permission will be obtained. In the case of direct quotations, these will be acknowledged by indication of the source if acceptable.

For pre-testing the instrument, consent was obtained prior to subject's participation. This was similar to annexure 1 but participants were informed that they are involved in a pilot study and the purpose for the pilot explained.

### 4.3.3 Data Analysis

The analysis of data is described with each relevant stage of the study.

### 4.3.4 Limitations of the Research Design

The final re-test phase of the instrument validation is not feasible and is beyond the scope of the present study. However, there are test-retest questions that were designed within the research tool in order to counteract this limitation. Other limitations of the study are specified under each stage of the study design.

## 4.4 Objective One

To develop an instrument that will be used to identify the GCP training needs for clinical researchers.

### 4.4.1 Instrument Development

Presently, no suitable instrument exists with which to identify training needs in the area of GCP (Truelove, 1995; Witkins, 1984; Payne, 1973).

As an aspect of the input component of the systems theory, the South African and International GCP factors are identified in relation to the GCP principles shown in annexure 14. The importance of a South African perspective on the development of the proposed instrument was discussed in the previous chapter. In this regard, key informants will form an important base input to the instrument development through knowledge of deficits that exist that come from experience in the field. Key informants will comprise experts from South African Universities, Ethics Committees, existing GCP trainers

and stake-holders which will include Medical Research Council (MRC), the Department of Health, the Drug Regulatory Authority, and the Medicines Control Council (MCC).

### 4.4.2 Steps in Instrument Development

- The topic or problem to be researched should be clearly defined: to provide a focus on which a design is based (McNiff et.al., 2000).
- The research scope should be specified. This step will inform the process of choosing a target population that will yield the desired information (McNiff et.al., 2000).
- Existing control system/laws should underpin this process – in this instance GCP and the regulatory bodies that subscribe to these guidelines (Department of Health, 2000).
- Consultation with stake-holders (Mouton, 1998).

Remaining abreast of recent literature in the field can make valuable contributions to the chosen approach, highlight more recent findings and contribute criticisms and limitations. This primarily informs the first step of instrument development (McNiff et.al., 2000; Marton,1975).

Once the above has been completed, the process of drafting the survey contents can begin. The survey will incorporate international and local GCP requirements. Specific elements will include knowledge application requirements, administration of informed consent, safety issues (reporting SAEs), drug handling, reports, data entry, intent to treat by physicians, patients compensation for injury, previous training attended, recommendations for future training and development in conducting clinical trials. In addition, participants will be asked what their perception of priorities in GCP training are (McNiff et.al , 2000; Marton,1975).

The use of key informants and brainstorming of sub-sections to be included in the questionnaire will be the second step (Gabbers, 1996). The outcome of this needs assessment data analysis will culminate in the grouping of questions and will be informed by the type of instrument that the researcher seeks to develop (Gabbers, 1996).

After sub-sections brainstorming, listing the key words, the key words will be listed under each sub-section. Whilst this is done, one will continuously evaluate if this is still in line with the topic and that the scope is adequately covered (Gabbers, 1996).

Once compiled, the initial instrument should be piloted to help guide final changes before implementation.

### 4.4.3 Development of an Instrument: Content

A modified questionnaire has been selected for use in training needs identification. Closed and open-ended questions, and other methods and scenarios will be included so as to facilitate the gathering of the desired information (Polit & Hungler, 1991).

The modified questionnaire will include verbal and written responses from the interviews conducted with the key informants. Based on the above sources, the content of the instrument should include the following sections:

#### 4.4.3.1 Patient Safety

Questions will explore the clinical researchers' knowledge on preparing applications for submission to the ethics committee paying particular attention to the informed consent documentation. Other areas will include drug handling (Foddy, 1994; Payne, 1973) and the management and reporting of AEs and SAEs. For the latter, a case scenario will be given for investigators to evaluate the reported serious adverse event.

#### 4.4.3.2 The Informed Consent

Interpretation of scenarios involving taking informed consent will be included as part of the tool. Particular attention will be given to identified problem area which include participants not being made

aware of all the elements of the study and in particular the areas of safety and potential lack of benefit (Newman, Pollock & Johnson-Thomson, 2003; Dal-re, 1992).

In addition to scenarios the clinical researcher will be asked to document what information the patient is being told during an informed consent session and the reason why.

#### 4.4.3.3 GCP Knowledge, Experience and Application

This will be explored using problem -solving approach with questions such as, “what to do if…

- a clinical trial participant (patient on a clinical trial) presents with unusual symptom;
- a clinical trial participant wants to withdraw from the study;
- a clinical trial participant has heard of a new drug in the market and want to try it;
- a clinical trial participants misses a scheduled visit or
- a clinical trial participant comes on an unscheduled visit or
- a clinical participant is unsure of how to complete a questionnaire”.

Some of these problem-solving skills and case scenarios will be addressing the “test and re-testing" aspect of the previously asked questions.

A section will determine whether respondents have knowledge of the South African guidelines and further request their input on issues being addressed by the South African GCP Guidelines, (please refer to annexure 4, section 6, question 5-7).

#### 4.4.3.4 Data quality

Areas to be explored will include:

- how would the clinical researcher prove that the patient exists and is not fabricated.
- provide evidence that no coercion was used.
- A scenario involving the discovery of an incorrect date of birth has been entered in case report form. The investigator will be asked how to correct this as well as how to prepare for monitor visits and audits.
- Frequency of protocol use and cross-referencing will be assessed. In addition, related questions on management of protocol deviation will be explored.

#### 4.4.3.5 Perceived Knowledge Gaps and Training Needs

Examples will include the following:

- Giving a scenario in which a draft protocol has been received for evaluation and recommendations and the investigator discovers that the standard of practice in the protocol is not compliant with local standards. How would the investigator respond by way of recommendation.
- Asking the clinical researcher to suggest the areas or topics that should be covered in a training model (Lo, Wolf & Berkeley, 2000; Foddy, 1994; WHO, 1994).

### 4.4.4 The Knowledge Score

The instrument will be designed in such a way that sections that target measurement of participants' GCP knowledge will be included, based on the content given in section 4.4.3 above. A score (the total score that each individual would have scored, if all the knowledge questions were answered correctly) is calculated.

The knowledge questions within the tool are those that required specific knowledge in specific areas of GCP. These areas included questions on informed consent, patient safety and clinical trials safety issues, quality data and specific clinical trial scenarios that required intervention by applying specific knowledge.

There are sections in the modified questionnaire that are selected to indicate the GCP knowledge (refer annexure 4 and sections specified below). These are as follows:

- Section 3 Question 2 (a-d): Specific Knowledge Scenarios
- Section 3 Question 3 (1&2): Patient Safety, Quality Data & Other
- Section 3 Question 6 (a-d): Informed Consent
- Section 4 Question 4 (a & b): Quality Data and Safety Issues

### 4.4.5 Data Analysis

Multivariate analysis will be used to establish the possible correlation of selected variables with knowledge scores. The assessment and analysis will include comparison of GCP trained versus untrained clinical researchers (principal investigators, sub-investigators, study co-ordinators and others, as specified by the respondents) and clinical researchers from various clinical practice areas.

## 4.5 The Key Informants

### 4.5.1 The Key Informant Sample

This population comprised 5 experts in the field of GCP and /or conduct of clinical trials, and were selected for convenience (Polit & Hungler, 1991). Experts were identified by the ethics committees, industry, universities and CRAs countrywide and represented all areas

and field in which clinical trials are conducted. The research tool for needs assessment will not be finalised until information from the key informants has been collected.

### 4.5.2 Steps to be followed for Key Informants Participation in the Study

- Telephonic request for an interview followed by fax or email confirmation will be followed by a clear explanation of the purpose of the interview.
- The reason and criteria for being selected as a key informant will be addressed. Confidentiality will be assured as no data will identify the participant by name (Booth, 1995; Leedy, 1993; Dal-re, 1992; Reynolds, 1982).
- Sampling will be purposive and convenient as key informants represent a scarce resource. A maximum of five key informants will be interviewed. To ensure coverage, at least one informant from Western Cape, KwaZulu-Natal and Gauteng will be included in the sample.
- Question were open in nature and identical for all informants. In essence these included questions on what in their opinion were the GCP training needs for clinical researchers, and reasons for those opinions. (Booth, 1995; Leedy, 1993; Dal-re, 1992; Reynolds,1982).

### 4.5.3 Key Informants Interviews: The Proposed Strategies for Analysis of Data

This qualitative data will then be collated and incorporated in the process of instrument development. Assistance will be sought form the Biostatistics Unit of the Medical Research Council and University of Western Cape.

### 4.5.4 Report from Key Informants Interviews

This data was collected during April and May 2003 and included five respondents. The content analysis resulted in the following:-

#### 4.5.4.1 Site Selection Screening Questions

It should be established if the investigator knows how to prepare the site facilities to ensure proper conduct of clinical trials. This would include the room and space, fridges and freezers and lockable cupboard to store medication of the clinical trial. These questions would ensure that the site selected would be able to comply with all study requirements.

Further, site preparation questions should include enquiring if the clinical researcher is able to ensure the patient population availability. For the proposed study, it should be established if there

are any competing studies, so as to exclude any conflict of interest and if there are any, if the investigator knows what to do in case of such situations.

#### 4.5.4.2 Time and Human Resources for Clinical Trials

The research instrument should establish how much time is allocated by the clinical researcher to attend to clinical trials and monitors. The same applies to the availability of staff as a support system and time to see the patients.

#### 4.5.4.3 Protocol Evaluation and Use

It should be established if the clinical researchers know how to evaluate a protocol for clinical trials so as to be able to use it correctly when conducting clinical trials.

#### 4.5.4.4 Writing of Source Data and Entering Data into Case Report File (CRF)

The key informants indicated that they felt clinical researchers have a gap in knowledge of writing the source data that will enable proper source data verification. The recommendation was to ask the clinical researchers if they know what Source Data Verification (SDV) entails so as to provide the source notes that will facilitate such a process.

#### 4.5.4.5 Informed Consent

The recommendations here were to establish if the clinical researchers know how to take informed consent, time spent during the procedure and elements of the informed consent.

#### 4.5.4.6 Adverse Events (A/E) and Serious Adverse Events (SAE)

It should be established if the clinical researchers know how to manage and report the adverse and serious adverse events.

#### 4.5.4.7 South African Guidelines for Conduct of Clinical Trials

It was recommended that the instrument should establish if the clinical researchers know about the South African Guidelines. To further establish if they apply these guidelines in the research setting, and to inquire if the clinical researchers had encountered any problems in applying these guidelines. Furthermore, to request any recommendations, pertaining to the South African guidelines from the respondents.

#### 4.5.4.8 Audits

To establish if the clinical researchers have experience of audits and to establish if these were executed by sponsors, regulatory authorities or the US Food Drug and Administration (FDA). If so, to

establish the clinical researchers' attitude towards audits and recommendations for other clinical researchers pertaining to audits.

#### 4.5.4.9 GCP Training

To establish if the clinical researchers have been trained for GCP. What kind of training was obtained (formal, informal or whatever). Duration of time since the last training, bearing in mind that one needs retraining every 18 – 24 months according to GCP requirements.

#### 4.5.4.10 Areas of Training

It was recommended that the clinical researchers should themselves indicate the areas where they need to be trained. This would ensure that clinical researchers are trained on the areas that have been identified by them.

The modified questionnaire for GCP training needs assessment was finalized after the input from the key informants, was incorporated. Before application, this instrument had to be tested on the same population that was going to participate in a survey.

### 4.6 The Pilot Study

#### 4.6.1 Sample for Pre-Testing of Instrument

The population for the pilot of the developed instrument for training needs assessment, comprised 10 practitioners in the field of

clinical research that use Good Clinical Practice, and as such are similar to the eventual study population, but were selected at random after the study participants for the survey of training needs.

### 4.6.2 Data Collection: Pilot Study

A pre-test of the instrument was carried out to ensure user friendliness, clarity of instructions and avoidance of ambiguity (Armstrong & Grace, 1994; Anderson, 1992; Polit & Hungler 1991). These points were then incorporated as necessary into the final draft of the instrument.

Ethical principles of consent to survey prospective participants, a full explanation of the study and assurance of confidentiality were adhered to in all stages of the study (Armstrong & Grace, 1994; Gillies, 1994; Anderson, 1992; Bell, 1989; McDowell & Newell, 1987; Bakana, 1971). The pre-testing of the instrument will be under direct control of the researcher.

### 4.6.3 Data Analysis Proposed Strategies: Pilot Study

Results of the pre-test were interpreted using the appropriate method that is directly related to the objective of the pilot study. Data was then collated and grouped. This information was then interpreted and corrective action taken, prior to implementation of the final questionnaire in the main study**.**

### 4.6.4 Pilot Study Data

This data was collected during the first week of June 2003. Most participants completed the questionnaires in the presence of the researcher but two questionnaires were faxed due to the distance between provinces and since this research was self-funded, costs were a consideration.

#### 4.6.4.1 Analysis and Interpretation of Pilot Study Data: Pilot Study Report

Of the ten selected respondents, six responses were received and usable. Two questions required rephrasing as follows:-

- **Section 1, Question 5: Please refer to annexure 3: Section 1, question 5**:

The initial question was phrased as one question, asking about the clinical researchers current position and further asking for how long he/she has been in that position. The responses indicated that it was difficult and confusing to give a single response to this question. To correct this; the question had to be rephrased and split into two questions, one enquiring about the respondent's current role in clinical trials and the second the time spent in their present position/role **Please refer to annexure 4: Section 1, question 5.**

- **Section 2, question 4; point number 2**: Please refer to annexure3: Section 2, question 4 “SDV” was not understood by some of the pilot study participants. To correct this; the question had to be rephrased and “SDV” had to be written in full as “ Source Data Verification” in the final tool. **Please refer to annexure 4: Section 1, question 5.**

After the analysis and interpretation of the pilot study data, the needs assessment instrument was then finalized for use in the survey of training needs

### 4.6.5 Ethical Aspect For Objective One

This was discussed at length in section 4.3.2, with specific reference to instrument development and participation of key informants.

## 4.7 Objective Two

To establish existing knowledge levels in clinical researchers by measuring their training needs using a survey.

### 4.7.1 Research Methodology for a Survey to Establish Training Needs

#### 4.7.1.1 The Population

The target population is all practitioners in the field of clinical trials who function as clinical investigators or study coordinators. For

the purpose of this study the term clinical researchers will be employed as their roles can be interchangeable. The total population is estimated to be approximately 300, based on the Ethics committees' database, investigator database from various pharmaceutical companies and universities.

#### 4.7.1.2 The Inclusion / Exclusion Criteria

**Inclusion Criteria**

The population to participate in the study includes all members of the research team that are known to be conducting clinical trials. The examples include study co-ordinators, data managers, principal investigators and sub-investigators.

**Exclusion Criteria**

Research personnel that are regarded as the service providers including staff members like radiographers and laboratory technicians who analyze blood samples, will not form part of the population being studied.

#### 4.7.1.3 Limitations of the Study Sample & Sampling Methods

A two stage sampling method was originally envisaged. Initially it was hoped that a full database of clinical investigators could be

obtained from the MCC or the Pharmaceutical Manufacturers Association (PMA), Clinical Trials Task Group (CTTG) and Pharmaceutical Physicians Association (PPA), but was either restricted as in the case of the MCC or unavailable.

As a compromise a list of potential participants was drawn from data that was available from pharmaceutical companies, academic institutions including institutional and private ethics committees, and finally the pool of investigators the researcher has had dealings with. This yielded a sample plate of 300 clinical researchers from which a random sample of 100 participants was drawn.



This sample size of 100 participants would allow for an example, proportions of researchers who follow the correct explanation on Serious Adverse Event; to be measured with an absolute precision of at least +/- 10% (Personal Communication with Dr. J. Levin, MRC Statistician: 21/01/2001 & 09/02/2005).

### 4.7.2 Data Collection

Using the developed instrument, data will be collected from 100 clinical researchers. A survey of training needs will be conducted, using a designed tool.

### 4.7.3 Data Analysis

The quantitative data will be entered into excel database and verified after response coding (see Annexure 5). Common answers will be grouped, interpreted and presented. Double data entry will be used to clear the data and to ensure that the data entered is correct.

Data analysis of frequencies and descriptive data will use the Stata statistical software package (Stata Statistical Software, 2001). Data collected from open-ended questions will be analysed, interpreted or coded and presented in narrative form.

#### 4.7.3.1 Analysis of Variance

This is a one-way analysis, which is used to compare the means of several groups (Kirkwood, 1988; Montgomery, 1976). This method is based on accessing how much of the overall variation in the data can be explained by differences between the group means, compared to the amount of variation due to differences between individuals in the same group (Kirkwood, 1988).

The total amount of variation is given by the sum of the squared deviations of observations about the overall mean. This sum of squares is partitioned into two distinct components:-

(i) The sum of squares due to differences between the group means.

(ii) The of squares due to differences between the observations within each group, also known as the residual sum of squares.

To calculate a variance we need to divide a sum of squares by the degrees of freedom (df). For a single group the degrees of freedom are the number of observations minus 1 (since this is what a sum of squares is divided by in order to obtain a variance).

The total degrees of freedom are divided into a between group degrees of freedom and a within group degrees of freedom. We can then calculate the amount of variation per degrees of freedom and this is called the mean square (ms).

The significance test, called the F-test or variance ratio test, is based on the comparison of the between groups and the within group mean squares.

If the observed differences between the groups were simply due to chance variation, the variation between these groups means would be about the same size as the variation between the individuals in the same group. Whilst if there were real differences the between groups variation would be larger.

Under the null hypothesis that there is no difference between the groups, the ratio of mean squares follows an F- distribution; the significance of the observed ratio can be assessed by the comparison with

the appropriate percentage points of the F-distribution. Note that this technique is equally applicable when the number of individuals in each group differs. This is done automatically by the stata package applied in this dissertation (Kirkwood, 1988).

#### 4.7.3.2 The Levels of Significance

There are three commonly used levels of significance, 5%, 1% and 0.1%. Results are usually classified as non-significant, significant at 5%, significant at 1% or significant at 0.1% (Mateo & Kirkhoff, 1999)

.

### 4.7.4 Ethical Aspects for a Survey

Principles outlined for the pilot phase of the study were adhered to in this phase of survey of training needs. Random sampling was employed and participants were entitled to the study results.

## 4.8 Objective Three: Development of a Training Model

This is the final phase of the study. The objective of this phase is to design and pilot a GCP training model for clinical researchers.

### 4.8.1 Model Development

This will be based on the recommendations on the results of the training needs survey.

The recommendations from key informants, will help in construction and modification of the training model. If the knowledge levels are established to be high, one will have to identify the source of information that led to this state of affairs.

### 4.8.2 Pre-testing a Training Model

Application of the designed training model on a large scale will not be feasible, however pre-testing the model on a smaller group is proposed, after input from the key informants on the model (Leedy, 1993; Polit & Hungler, 1991).

### 4.8.3 Sampling for Pre-testing the Training Model

The original sampling frame will be used. A random sample of ten participants is proposed, that will be selected from the remaining subjects, who neither participated in the instrument testing nor its application (Leedy, 1993; Polit & Hungler, 1991).

The results of the key informants' input will be analysed and applied to the model before moving to the next stage of the study, which is finalisation of a training model.

### 4.8.4 Finalising the Training Model

Based on the results of the pilot study, expert recommendations and additional recommendations of Regulatory Authorities (MCC) and Ethics Committees, the model will be modified before finalisation.

The principles of adult education and outcome-based education will guide the training model. The SAQA (South African Qualification Association) guidelines will be followed to ensure that the model and the providers meet criteria for future accreditation (Duant, 2003; Jarvis, 1996; Roberts-DeGennaro, 1996; Jones & Mann, 1992; Knowles, 1980).

### 4.8.5 Criteria for an Ideal Model

These will be identified from literature pertaining to the justification of the model presented in chapter 7 (Johnson, 1974).

## 4.9 Conclusion

This chapter has described the research design, the methodology for achieving each objective and dealt with aspects such as ethics, validity and reliability for each objective of this study. The following chapter presents the findings from the implementation of the survey of needs assessment on GCP knowledge and reported practice.

# CHAPTER 5

## DATA ANALYSES AND INTERPRETATION

### 5.1 Introduction

Data presented here are in respect of study objective 2, namely training needs assessment using the developed instrument. The data collected on pre-testing the proposed model for training in GCP, will be analysed in chapter seven.

### 5.2 Realisation of the Study

The writer, as indicated in the methodology chapter, directly collected the data. The process took longer than expected due to the problems encountered. These problems included the following:

- Proposed participants being off-duty or on leave thus not available at the known address. This led to rescheduling of appointments where possible, or exclusion from the study.
- Proposed participant being off sick and unavailable for the duration of the data collection period thus unable to participate. Although this applied to four out of 100 randomized participants, it did affect the number of responses at hand.
- Busy practices leading to constant re-scheduling of appointments to the extent that it was impossible to continue with re-scheduled dates, if the study was to be completed.

- Blank / uncompleted questionnaires: as much as the initial plan was to let the respondent complete the questionnaire in the presence of the researcher, it so happened that there were situations that the potential respondent expected to be free at a particular time, only to find the patients doing late bookings which had to be accommodated. This was seen mostly in busy private practices.

There were two types of non-responses namely:-

- the unit non-response
- the item non-response (Kirkwood, 1988).

**The unit non-response** means that the whole questionnaire was uncompleted. Of 100 randomised participants, 16 questionnaires were classified as unit non-response, leaving an evaluable sample of 84.

**The item non-response–** this is the situation whereby certain questions in the questionnaire were not completed. In this study, the number of missing answers to any question ranged from 0 –19. Some questions were not applicable to certain respondents and some respondents choose not to answer certain questions (Kirkwood, 1988).

In situations of blank and uncompleted questionnaires; the researcher was asked by the potential participants to leave a questionnaire so as to allow the participant to complete it in between

patient appointments. The arrangement was to collect the completed questionnaire at the time agreed upon or suggested by the participants. When the time for collection arrived most of these questionnaires had not been completed and were returned blank. As participation was voluntary, these kinds of scenarios could not be questioned nor participation enforced.

- Although the researcher ended up re-scheduling some appointments, it was discovered that the response rate was better in academic / university and public sector environments. The same trend of better compliance was also seen in research driven sectors.

## 5.3 Survey Data: Findings

### 5.3.1 Section I: Socio-demographic Data

#### 5.3.1.1 Gender Distribution

More female than male respondents participated as shown table 5.1

**Table 5.1 Male and Female Respondents:**

| Gender | No. Of Respondents | Percent |
|---|---|---|
| Male | 29 | 34.5 |
| Female | 55 | 65.5 |
| **Total** | **84** | **100.00** |

This reflects the gender distribution of clinical researchers with the majority of study co-ordinators being female.

### 5.3.1.2 Qualifications of Respondents

The respondents were given a list of Qualifications from which to select their highest qualification (see Figure 5.1). “Other” qualification was given as an option for those who had qualifications that were not listed. If other was chosen as a response, the respondents were asked to specify the other qualification. Since those that had ticked other were asked to specify “other”, this was further categorised as per table 5.2 on the next page. The coloured text indicates the breakdown of “other”.

**Fig. 5.1 Showing Highest Qualification of Respondents**

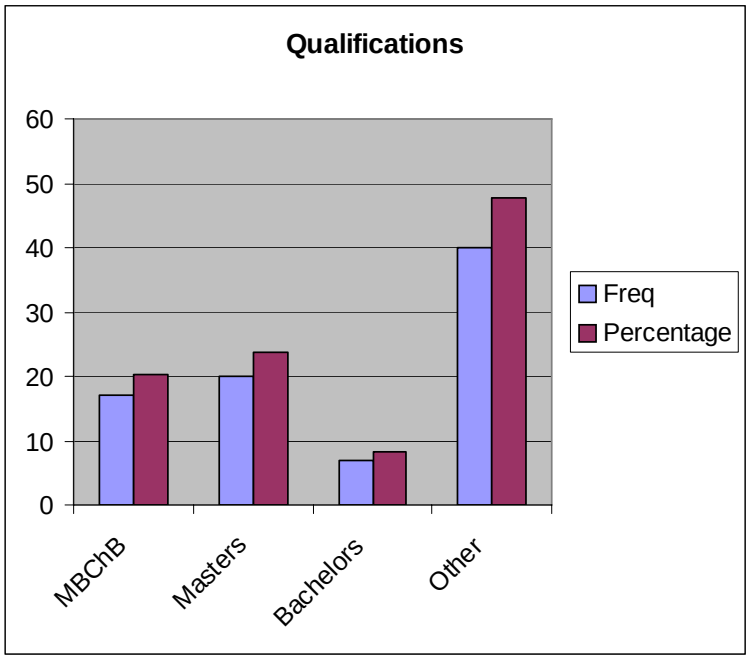


**Table 5.2 Respondents' Highest Qualifications including "other" qualification specified in colour:**

| Qualifications | No. Of Respondents | Percent |
|---|---|---|
| MBChB | 17 | 20.24 |
| Masters | 20 | 23.81 |
| Bachelors | 7 | 8.33 |
| Nursing | 16 | 19.05 |
| Fell.Col. Phys. | 5 | 5.96 |
| Radiology diploma | 3 | 3.57 |
| National diploma | 3 | 3.57 |
| Clin. & Med. Tech. | 2 | 2.38 |
| Matriculation | 2 | 2.38 |
| Unspecified | 6 | 7.14 |
| PhD | 2 | 2.38 |
| Labour Law diploma | 1 | 1.19 |
| **Total** | **84** | **100.00** |

The distribution was as follows:-

17 (20.24%) had MBChB degree

20 (23.81%) had Masters degrees

7 (8.33%) had Bachelor's Degree

40 (47.62%) had other qualifications.

Other qualifications included, nursing diploma, Fellow of college physicians, radiology diploma, national diploma, clinical and medical technology, PhD and matriculation. Six did not specify their qualifications. The nursing diploma participants were sixteen, which was the most frequent amongst other categories.

#### 5.3.1.3 Area of Practice of Respondents

The respondents were asked to indicate their area of practice. Areas listed were private, public or academic and other. For other, the respondents had to specify the area. The responses were as follows:-

24 respondents were in both private and public sectors

14 respondents in private sector only

34 respondents in public sector only

12 respondents in neither public nor private but regarded themselves as working in other categories. The other categories were respondents from provincial hospitals (ten respondents) and military hospitals (two respondents).

#### 5.3.1.4 Current Involvement with Clinical Trials

One of the questions inquired if the participants were currently involved in conducting clinical trials. Of 84 respondents, 83 (98.81%) were currently involved with clinical trials.

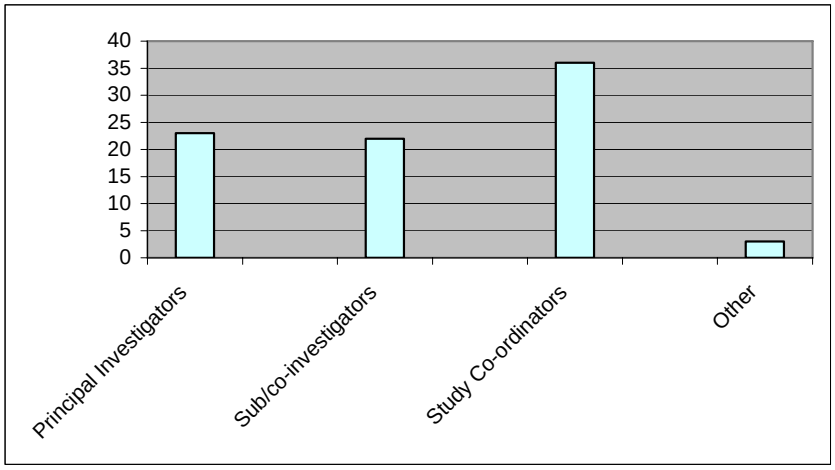
### 5.3.1.5 Current Role of Respondents

Each respondent was asked about his / her current role in the conduct of clinical trials, namely:-

1. Principal investigator
2. Study co-ordinator
3. Sub / co- investigator
4. Other.

Other was given as the fourth option, and if one had selected other, one had to specify the other category. The distribution of roles was as indicated in figure 5.2.

**Figure 5.2 Clinical Researchers' Current Role in Clinical Trials:**




Most respondents were functioning as study co-ordinators. Since there was other category, the three specified other were

research scientist, data manager and trial assistant as shown above.

#### 5.3.1.6 Duration in Years - Involvement with Clinical Research

The participants were asked how long they had been involved with clinical trials. The responses varied from 0.25 year (3months), to 28 years. The mean was 5.2 years and the median was 5 years.

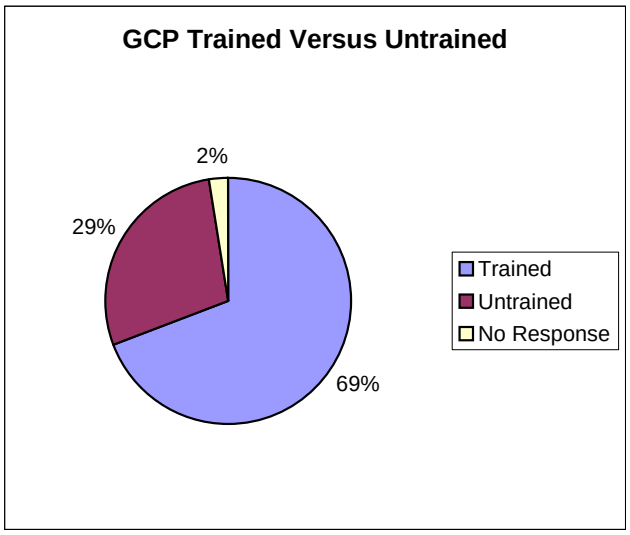
### 5.3.2 Section II - GCP Knowledge

This section contained five items that were phrased as shown in the following subheadings:

#### 5.3.2.1 GCP trained and Untrained Respondents

The first question had to establish amongst the participants which ones were GCP trained and those that were untrained. The response is as shown in figure 5.3.

**Figure 5.3 GCP Trained and Untrained Respondents :**




The majority of respondents were GCP trained forming 69.05%. Although the number of untrained respondents appears to be low being 28.57%, it is

quite important when one acknowledges that GCP is the foundation that clinical research is based upon. The two groups will be further explored later in this chapter.

#### 5.3.2.2 How Training or Knowledge was Obtained

(a) The respondents were asked how they obtained their training or acquired their knowledge. The responses are shown in table 5.3:-

**Table 5.3 How GCP Knowledge Was Acquired**

| **Type of Training** | **No. of Respondents** |
|---|---|
| None of all four items | 10 |
| Formal Training Only | 10 |
| Informal Training Only | 15 |
| Reading Material on GCP Only | 3 |
| Other Only | 2 |
| Formal & Informal Training | 6 |
| Formal; Informal Training & Reading Material on GCP | 19 |
| Informal Training; Reading Material on GCP & Other | 1 |
| Informal Training & Reading Material on GCP | 10 |
| Informal Training; Reading Material on GCP & other | 1 |
| Informal Training and Other | 1 |
| Reading Material on GCP & Other | 1 |
| Formal; Informal Training; Reading Material on GCP Other | 5 |
| | 84 |

Note: Other ways of obtaining knowledge included in-service training, information from colleagues, training from the ethics committees and getting information through internet.

#### 5.3.2.3 Need for More GCP Training

The third question inquired if the participants felt that they needed more training on GCP or not. Further to this, each respondent was asked to substantiate his / her response.

**Table 5.4 Need or No Need for Training:**

| Training Need | No. of Respondents | Percent |
|---|---|---|
| No answer | 2 | 1.20 |
| Need for training | 62 | 74.70 |
| No need for training | 20 | 24.10 |
| **Total** | **84** | **100.00** |

Sixty- two respondents (74%) indicated that they need more training in GCP whilst 20 (24%) felt there was no need for training. The remaining 2% of participants did not respond to this question.

A further question was asked to establish the reason for the above response. Of the 84 respondents, (52%) did not give a reason. The reasons given by the remaining respondents included those who felt no need because of the following reasons:-

- They perceived themselves as having a lot of experience,
- had recent training or were going to go for training soon,
- felt GCP training is being repeated during start-up meetings,
- one thought most GCP issues are common sense.

Those who had a need for training indicated that they need regular updates as an ongoing process and refresher courses especially when new information becomes available, to get current updates, never had formal training before, needed proper training of what is acceptable, and to update knowledge at least two yearly so as to give best service, were all reasons for necessitating training.

#### 5.3.2.4 Areas of Training

Seven areas were listed in which respondents were required to check all the applicable areas where he / she needed training. All items listed in the questionnaire except investigator responsibility, were ticked.



#### 5.3.2.5 Other Need for Training

The areas of training as perceived by the clinical researchers included those listed under section 5.3.2.4.

Those who selected other were further asked to specify the other areas. These will be discussed after figure 5.4 to follow.

**Fig.5.4 Perceived Need in Areas of training**


1 = Informed Consent

2 = Source Data Verification

3. = Investigator responsibility

4. = Study Agreements

5. = Patient safety

6. = Quality assurance

7. = Data Handling

8. = Others

Other aspects (no.8) included training for FDA audits, electronic data capture, time management and update on South African guidelines to conduct clinical trials.

#### 5.3.2.6 Additional Information to be Included in Planned GCP Training Model

The participants were asked if they had suggestions of additional information that should be included in the planned GCP training model.

**Table 5.5 Additional Information to be Included in a Planned GCP Training Model:**

| Suggestions | No. of Respondents | Percent |
|---|---|---|
| No response (blank) | 15 | 17.86 |
| Suggested Topics "yes" | 15 | 17.86 |
| No Topics (ticked "no") | 54 | 64.29 |
| **Total** | **84** | **100.00** |

The respondents were expected to tick against an appropriate box indicating: "Yes =1" or "No = 2", as indicated in table 5.5, above. There were 54 respondents who ticked "no" and made no suggestions. There were 15 respondents who ticked neither "yes nor no", leaving the response blank. Lastly, there are 15 respondents who ticked "yes", indicating that they do have suggestions on topics to be included in the planned training model. A further request was made for participants to specify the additional information to be included in

the planned GCP training model. Most respondents did not specify the area of additional information. Suggested Information for inclusion in planned GCP training model included the following:

- Electronic data capture
- Ethics involvement in trials
- MCC applications
- Recruitment strategies and ethics role in clinical trials

#### 5.3.2.7 Time Allocated to be Spent with the Monitor

The participants were asked how much time they were allocated to spend with monitors at the investigator site. The listed responses to choose from ranged from none, 1-2 hours, 3-4 hours to .5 day (half a day). Then other was put as the 5th option. The responses were recorded in table 5.6. Other times are specified in table 5.7 to follow:

**Table 5.6 Time Spent with the Monitor:**

| Time Spent | No. of Respondents |
|---|---|
| 0 hours | 1 |
| 1-2 hours | 24 |
| 3-4 hours | 8 |
| Half a day | 18 |
| Other time | 20 |
| No response | 13 |

**Table 5.7 Other Times are Summarised:**

| Other Times | No. of Respondents |
|---|---|
| None specified time | 04 |
| 1 hour as required | 06 |
| 1-2 hrs/week | 01 |
| 12 hrs/month | 01 |
| 1 day as required | 03 |
| According to trial / CRA needs | 02 |
| As required | 03 |

### 5.3.3 Section III -Knowledge and Application of GCP

#### 5.3.3.1 Knowledge Questions on Handling of the Following Scenarios

Scenarios were sketched and requested respondents to indicate their chosen handling of the situation. These scenarios included:

(a) A patient presents with an unusual symptom

(b) A patient misses a visit

(c) A patient wants to withdraw from the study

(d) A patient is unsure of how to complete a questionnaire.

Values (marks) were allocated as 1 for the full correct answer and half a mark (.5) for the partially correct or incomplete answer as indicated in table 5.8 (a) below.

**Table 5.8 (a) Response to Scenario – Unusual Symptom:**

| Unusual symptom | No. of Respondents | Percent |
|---|---|---|
| 0 (incorrect answer | 56 | 66.67 |
| .5 (answer correct but incomplete) | 01 | 1.19 |
| 1 (correct answer) | 27 | 32.14 |
| **Total** | **84** | **100.00** |

From these results, one can identify that knowledge on how to manage these scenarios was lacking, in 56 (66.67%) of respondents.

**Table 5.8 (b) Responses to Scenario – Missed Visit:**

| Missed visit | No. of Respondents | Percent |
|---|---|---|
| Incorrect answer | 48 | 57.14 |
| Correct answer | 36 | 42.86 |
| **Total** | **84** | **100.00** |

Out of 84 respondents, 36 (42.86%) got the answer correct. This is another apparent knowledge gap indicating that the training need is present in 48 (57.14%) of respondents.

**Table 5.8 (c) Responses to Scenario – Consent Withdrawal:**

| Withdrawn Consent | No. of Respondents | Percent |
|---|---|---|
| Incorrect answer | 53 | 63.10 |
| Correct answer | 31 | 36.90 |
| **Total** | **84** | **100.00** |

Out of 84 respondents, 31 (36.9%) got the answer correct. Some of the wrong answers included convincing the patient to stay in the study, re-consenting. Other indicated that one should try and discourage the patient not to withdraw. Some researchers indicated that one should inform the Principal Investigator or study co-ordinator respectively and establish if the patient can be withdrawn. Some would say withdraw the patient without questions. This is an apparent knowledge gap in 53 (63.10%) of respondents.

**Table 5.8 (d) Responses to Scenario – Unsure of How to Complete a Questionnaire:**

| Questionnaire | No. of Respondents | Percent |
|---|---|---|
| Incorrect answer | 54 | 64.29 |
| Correct answer | 30 | 35.71 |
| **Total** | **84** | **100.00** |

Out of 84 respondents, 30 (35.71%) got the answer correct. This is an apparent knowledge gap for 54 (64.29%) of respondents.

#### 5.3.3.2 Aims of GCP

The respondents were asked to state the two aims of GCP. The commonly given responses were patient safety and quality data. The responses were grouped and tabulated according to the two common response groups (quality data and patient safety). Other responses were grouped as "other" aims of GCP as shown on table 5.9 c.

**Table 5.9 (a) Summary of Results on Respondents who got a Correct Answer – Quality Data:**

| Quality Data | No. of Respondents | Percent |
|---|---|---|
| Incorrect answer | 43 | 51.19 |
| Correct answer | 41 | 48.81 |
| **Total** | **84** | **100.00** |

**Table 5.9 (b) Summary of Respondents who stated Patients' Safety as Correct Answer**

| Patient Safety | No. of Respondents | Percent |
|---|---|---|
| Incorrect answer | 34 | 40.48 |
| Correct answer | 50 | 59.52 |
| **Total** | **84** | **100.00** |

This table shows 50 (59.52%) out of 84 got the answer correct. This is an apparent knowledge gap. Patient safety is an important aspect of GCP that every clinical researcher is expected to know.

**Table 5.9 (c) Responses on Other Aims of GCP**

| Other | No. of Respondents | Percent |
|---|---|---|
| Incorrect answer | 81 | 96.43 |
| Correct answer | 3 | 3.57 |
| **Total** | **84** | **100.00** |

### 5.3.3.3 Types of Agreements

Here respondents were asked to name two kinds of agreements that the investigator signs before or during study initiation. The common responses were:



**Tables 5.10 Responses indicating Types of Agreement:**

| Types of Agreement | No. of Respondents |
|---|---|
| Confidentiality agreement | 42 |
| Financial agreement | 47 |
| Protocol Agreement | 12 |
| Other (Standard Clarification Agreement) | 2 |

Forty-two respondents mentioned confidentiality agreement, 47 respondents mentioned financial agreement, 12 mentioned protocol agreement and two respondents mentioned other. Two respondents mentioned other agreements that are pharmaceutical industry specific.

#### 5.3.3.4 Additional Information to be Included in Planned Model

The respondents were asked if they had any suggestions for additional information to be included in the planned GCP training model. This was a repeat question that was purposely done to test and retest the previous response in section 2, question 5. See table (5.11a)

**Table 5.11 (a)**

**Suggested Additional Information - Suggestions and No Suggestions:**

| Suggestions | No. of Respondents | Percent |
|---|---|---|
| No response | 7 | 8.33 |
| Suggestions = 1 | 14 | 16.67 |
| No suggestions = 2 | 63 | 75.00 |
| **Total** | **84** | **100.00** |

Out of 84 respondents, 14 (16.67%) indicated that they have suggestions of areas to be included in the planned GCP training model. Other 63 had no suggestions whilst seven did not respond. Those that had no suggestions ticked “no” under any suggestions, whilst those that did not respond returned the questionnaire with neither “yes nor no” ticked. This was an item none response, discussed in section 5.2.

**Table 5.11 (b) The Suggested Areas / Topics to be Covered on Planned Training Model - Specified topics:**

| Suggested Topics | No. of Respondents |
|---|---|
| No response | 76 |
| GCP updates | 1 |
| Role definition | 1 |
| Study agreements | 1 |
| Time management | 1 |
| SA Guidelines | 1 |
| MCC role | 1 |
| 3rd world research | 1 |
| Best practice debate | 1 |
| **Total** | **84** |



### 5.3.3.5 Informed Consent Knowledge and Application

The respondents were asked questions exploring if the correct procedure is followed during the informed consent process. Refer annexure 4: Section 3, question 6.

**(a) Inviting Statement as Part of Informed Consent**

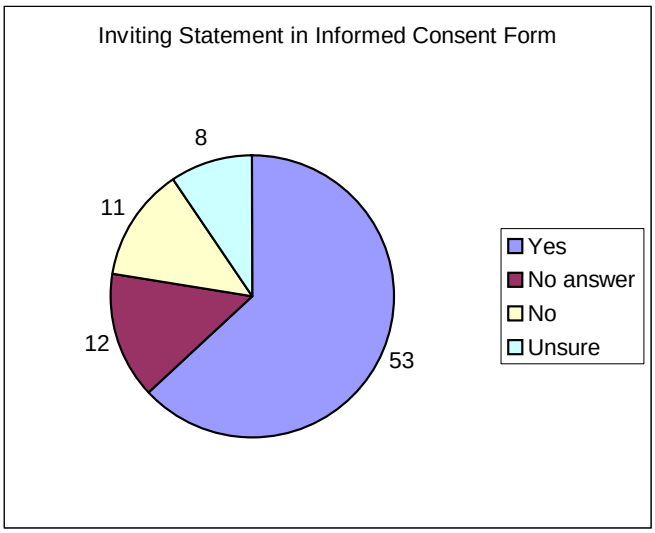
The respondents were asked if they would include an invitation to prospective participants to participate in the clinical trial.

See table 5.12 (a) and figure 5.5 for the responses.

**Table 5.12 (a) Inviting Statement for Prospective Trial Participant – Informed Consent Form:**

| Informed Consent Form | No. of Respondents |
|---|---|
| Did not answer | 12 |
| Would include a statement | 53 |
| Will not include a statement | 11 |
| Were unsure of what to do | 8 |

**Figure 5.5 Inviting Statement in the Informed Consent**




**(b) What Precedes Trial Patients' Involvement in the Clinical Trial**

The participants were given list of four topics / things that should precede clinical trial patient participation in a clinical trial. This is shown in annexure 4 (final research tool).

1) Sixty-one (72.60%) respondents would conduct verbal explanation before enrolling the patient into a clinical trial.

(2) Seventy-four (88.1%) respondents would start by giving the patient the IL and get a signed IC before enrolling the patient into the study.

(3) Forty-four (52.38%) would precede patient enrolment by a written document. This is a knowledge gap for clinical researchers. Forty (47.62%) respondents did not indicate that they would proceed with a written document.

(4) Out of 84 respondents, 31 (37.35%) would start with a study procedure before patient's enrolment in a clinical trial. There is a training need for these clinical researchers as this is a requirement for GCP. It is not allowed to conduct any study related procedure before getting an informed consent. This includes both verbal explanation and written document.

#### 5.3.3.6 Risks and Benefits of Participating in a Clinical Trial

Respondents were asked if they would tell the patients about risks of participating in clinical trials and were requested to give reasons for doing so. Out of 84 respondents that indicated they would tell the participants about risks and benefits, fourteen (17 %) specified the reasons for telling the patients about the risks and benefits as shown in table 5.12b.

**Table 5.12 (b) Reasons for Informing the Patient about Risks Involved on Participating in Clinical Trial: Risks**

| Reasons | No. of Respondents | Percent |
|---|---|---|
| Response left blank | 70 | 83.33 |
| No reason given | 1 | 1.19 |
| Adverse events | 1 | 1.19 |
| Contact Re: Problems for Awareness | 1 | 1.19 |
| GCP requirement | 1 | 1.19 |
| For informed decision | 5 | 5.95 |
| For patient awareness | 1 | 1.19 |
| Patient's right | 2 | 2.38 |
| Side effects | 2 | 2.38 |
| **Total** | **84** | **100.00** |

**Table 5.12 (c) Responses as Whether the Clinical Researcher will inform the Patient about the Benefits:**

| Benefit | No. of Respondents | Percent |
|---|---|---|
| No response | 12 | 14.29 |
| Yes (would tell pt about benefits) | 71 | 84.52 |
| No (would not tell the patient about benefits) | 1 | 1.19 |
| **Total** | **84** | **100.00** |

The participants were asked to indicate if they would tell the participants about the benefits of participating in clinical trials. The response was as per table 5.12c. The respondents were also requested to substantiate reasons for their given responses. These are shown in table 5.12 (d), below:-

**Table 5.12 (d) Reasons for Telling the Patient about the Benefits:**

| Reason | No. of Respondents | Percent |
|---|---|---|
| No reason given | 79 | 94.05 |
| Advantages of research | 1 | 1.19 |
| Holistic healthcare | 1 | 1.19 |
| Proper decision | 2 | 2.38 |
| Understand why trial is done | 1 | 1.19 |
| **Total** | **84** | **100.00** |

#### 5.3.3.7 Patient Given a Copy of Informed Consent

The respondents were asked why trial participant should be given a copy of the signed informed consent. Responses included:

**a) Legal Reasons**

Thirty (35.71%) indicated that the patient should be given a signed informed consent copy for legal reasons. This shows a training need or a gap in knowledge pertaining to the informed consent for clinical trial because a copy given to the participant in the trial protects the clinical researcher in a sense that it is an indication of non-coercion in participation.

**(b) Referral Purposes**

Out of 84 respondents, 35 (41.67%) indicated that the patients should be given a copy for future referral purposes. This shows a deficit in knowledge. All clinical researchers must be aware of this reason, thus it is an area requiring correction to practice.

### 5.3.4 Section 4: Data Quality & Safety

#### 5.3.4.1 Declaration of Helsinki

The participants were asked if they were well versed regarding the content of the Declaration of Helsinki (2000). The response was as seen in table 5.13.



**Table 5.13 Knowledge of the Declaration of Helsinki (2000):**

| Declaration Of Helsinki | No. of Respondents | Percent |
|---|---|---|
| No response | 13 | 15.48 |
| Yes | 40 | 47.62 |
| No | 31 | 36.90 |
| **Total** | **84** | **100.00** |

The above table 5.13, indicates that 31 (36.9%) of the clinical researchers, did not know the provisions of the Declaration of Helsinki (Department of Health, 2000).

### 5.3.4.2 Handling of Serious Adverse Events (SAE)

The respondents were asked to specify the time frame for reporting a Serious Adverse Event (SAE). Out of 84 respondents, 56 (66.67%) correctly defined the time frames for reporting, however, the balance, albeit the minority, form a substantial number of clinical trial staff who are not aware of some of the basic safety procedures necessary to safely conduct a clinical trial.

### 5.3.4.3 Supply of a GCP Document to Clinical Researchers by Sponsor

**Table 5.14 Respondents that were Supplied with GCP Document by the Sponsor**

| GCP Copy | Frequency | Percent |
|---|---|---|
| No response | 14 | 16.67 |
| Yes | 41 | 48.81 |
| No | 29 | 34.52 |
| **Total** | **84** | **100.00** |

The respondents were asked if the sponsor supplies them with a copy of GCP. The responses given in table 5.14 showed that 29 (34.52%) indicated that the sponsor does not supply them with a copy of GCP, Fourteen (48.81%) indicated that they do get a supply. Fourteen (16.67%) did not respond. It is therefore possible that 50%

of clinical researchers may not be provided with a copy of GCP Guidelines.

#### 5.3.4.4 Data Handling and Patient Safety Scenarios

**Table 5.15 (a) Correct and Incorrect Answers - Case Report Form (CRF) Data Handling:**

| CRF Handling | No. of Respondents | Percent |
|---|---|---|
| Wrong answer | 26 | 30.95 |
| Incomplete | 4 | 4.76 |
| Correct Answer | 54 | 64.29 |
| **Total** | **84** | **100.00** |

Of the 84 respondents, 54 (64.29%) answered correctly whilst 4were partially correct and 26 (30.95%) got the answer incorrect.

**(b) A Known Adverse Event Becomes Serious**

The participants were asked what they would do if the adverse event becomes serious. Responses were marked as incorrect or correct as shown in table 5.15 (b):

**Table 5.15 (b) Incorrect and Correct Answers on Reporting SAE:**

| SAE | No. of Respondents | Percent |
|---|---|---|
| Incorrect | 21 | 25.00 |
| Correct Answer | 63 | 75.00 |
| **Total** | **84** | **100.00** |

Out of 84 respondents, 63 (75%) got the answer correct whilst 21 (25%), got it incorrect. This is a knowledge gap in the case of 21 (25%) of clinical researchers at the time of the study.

**5.3.4.4 Notifications re-SAE**

**Table 5.16 Responses about Notifications for SAE:**

| SAE: Reporting | No. of Respondents | Percent |
|---|---|---|
| Incorrect answer | 27 | 32.14 |
| Ethics | 51 | 60.71 |
| MCC | 6 | 7.14 |
| **Total** | **84** | **100.00** |

The respondents were asked who, apart from sponsor, should be notified of an SAE. Fifty-one (60.71%) of respondents indicated that the Ethics committee should be notified. This was the expected answer. Twenty-seven (32.14 %) got the answer wrong whilst six (7.14%) indicated that the Medicines Control Council (MCC) should be notified. This was not an expected answer since it is the sponsor responsibility to notify the MCC. This answer was however not rejected because there are certain circumstances e.g. investigator driven studies, whereby the investigator site do have the responsibility of notifying the MCC.

**5.3.4.6 Ability to do Ethics Application**

The respondents were asked if they have completed and submitted an application to an ethics committee for approval to conduct a clinical trial. A minority, 39 (46%) of respondents reported that they had completed and submitted an application to an ethics committee, suggesting a challenge in respect of training need, given that this remains the primary responsibility of the investigator for his/her particular site. Thirty-five respondents (41.67%), have never completed and submitted an ethics application before whilst 10

participants (11.9%), did not answer this question. This is a training need because it is the investigator site responsibility to submit these applications.

#### 5.3.4.7 Explanation Given to Patients About the Procedures Involved in the Study

Respondents were asked if they would explain about all the study-related procedures that would be relevant. To this question, 74 (88.10%) of responses were in the affirmative.

#### 5.3.4.8 Explaining the Risks / Benefits of participating in the Study

The participants were asked if they would tell the trial patients about the risks and benefits of participating in a clinical trial. This was a test-retest question.

Out of 84 participants, 64 (76.19%) indicated that they would tell the patient about risks / benefits of participating in a clinical trial. One respondent would not tell whilst 19 (22.62%) participants did not respond to this question. Reasons provided for their responses are provide in table 5.17 below, that also indicates 71 (84,52%) that did not respond, despite 64 (76,19%) saying they do tell patient participants about risks and benefits.

**Table 5.17 Reasons for Telling / Not Telling the Patient about the Risks / Benefits of Participating in a Clinical Trial:**

| Reason | No. of Respondents | Percent |
|---|---|---|
| No response | 71 | 84.52 |
| Ensure compliance | 1 | 1.19 |
| GCP requirement | 1 | 1.19 |
| Informed decision | 5 | 5.95 |
| Investigator Duty | 1 | 1.19 |
| Chances of placebo | 1 | 1.19 |
| Side effects | 1 | 1.19 |
| Patients' right | 1 | 1.19 |
| Create awareness | 2 | 2.38 |
| **Total** | **84** | **100.00** |

### 5.3.4.9 Copies of Informed Consent

The respondents were asked why they should have 2 copies of informed consents

**Table 5.18 (a) Responses that Stated Copy For Patient:**

| Patient copy | No. of Respondents | Percent |
|---|---|---|
| No | 28 | 33.33 |
| Yes | 56 | 66.67 |
| **Total** | **84** | **100.00** |

**Table 5.19 (b) Responses that Stated Investigator File Copy:**

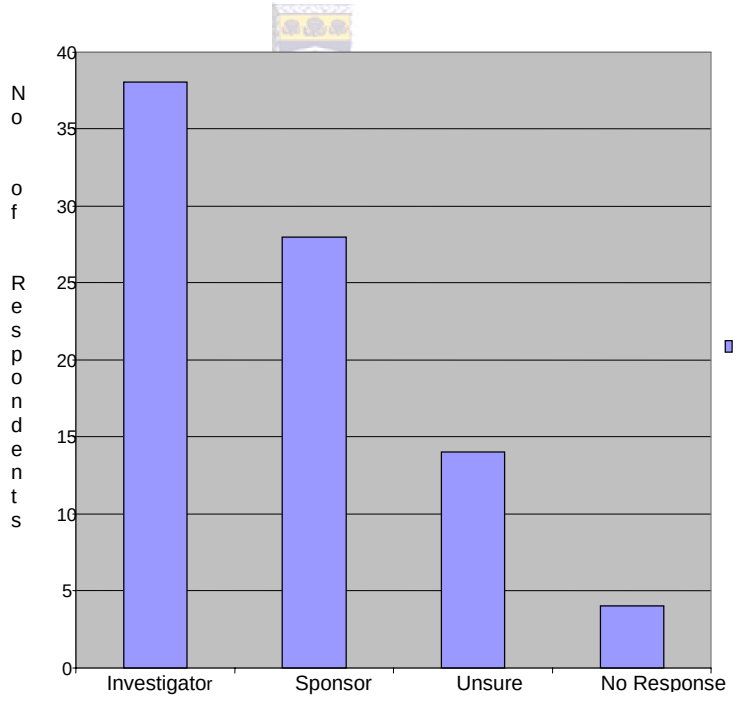
| Investigator file | No. of Respondents | Percent |
|---|---|---|
| No | 29 | 34.52 |
| Yes | 55 | 65.48 |
| **Total** | **84** | **100.00** |

This shows knowledge deficit and training need for the clinical researchers. It is important to know that the clinical researchers practice giving a copy of informed consent to trial patient, but more important to know if they have insight as to why such a practice required.

### 5.3.4.10 Responsibility for Ethics Application

The respondents were asked to choose whom of the sponsor, or the investigator, was responsible for ethics applications.

**Figure 5.6 Responsibility for Ethics Application:**



Out of 84 respondents, 38 (45.24%) got the answer correct according to GCP requirements; it is the investigators' responsibility to do Ethics application. Please see responses displayed in figure 5.6.

### 5.3.5 Section 5: Attitude Questions

#### 5.3.5.1 Clinical Investigators' Attitude

South African clinical investigators have mixed attitude towards the following current concerns; these are contentious issues for which each has proponents and opponents. In spite of the physicians association, industry representatives and the clinical trial task group meeting, the following issues remain unresolved and continue to be debated: -

- Financial interest disclosure to MCC & Ethics
- Placebo-controlled trials
- Supply of medication to patients post trial
- MCC interest in the number of studies each investigator site is conducting.

The participants were asked to indicate how they felt about the above issues with responses being dichotomised as either positive (in favour of the situation) or negative (against the situation/scenario). The following four tables: 5.20a; 21b; 22c & 22d show the responses to the four sub-headings that were explored.

**Table 5. 20 (a) Positive and Negative Responses - Financial Disclosure:**

| Financial Disclosure | No. of Respondents | Percent |
|---|---|---|
| No response | 41 | 48.81 |
| Positive | 36 | 42.86 |
| Negative | 7 | 8.33 |
| **Total** | **84** | **100.00** |

**Table 5. 21 (b) Positive and Negative Responses - Placebo Controlled Trials:**

| Placebo controlled trial | No. of Respondents | Percent |
|---|---|---|
| No response | 45 | 53.57 |
| Positive | 31 | 36.90 |
| Negative | 8 | 9.52 |
| **Total** | **84** | **100.00** |

**Table 5.22 (c) Positive and Negative Responses - Supply of Medication to Patients Post Trial:**

| Post Trial Medicine Supply | No. of Respondents | Percent |
|---|---|---|
| No response | 35 | 41.67 |
| Positive | 48 | 57.14 |
| Negative | 1 | 1.19 |
| **Total** | **84** | **100.00** |

**Table 5. 22 (d) Positive and Negative Responses: MCC's Interest in the Number of Trials per Investigator Site:**

| MCC's & Trials | No. of Respondents | Percent |
|---|---|---|
| No response | 45 | 53.57 |
| Positive | 36 | 42.86 |
| Negative | 3 | 3.57 |
| **Total** | **84** | **100.00** |

The above four tables show the responses towards each sub-category. The categories show either positive, which is for the idea; or negative, which is against the idea. There are those that gave no response; approximately half of the respondents had no apparent views on the three of the issues.

Out of the four categories, it is the post trial medication for patients that was most favoured by the respondents with a positive response of 57.14% (table 5.22c).

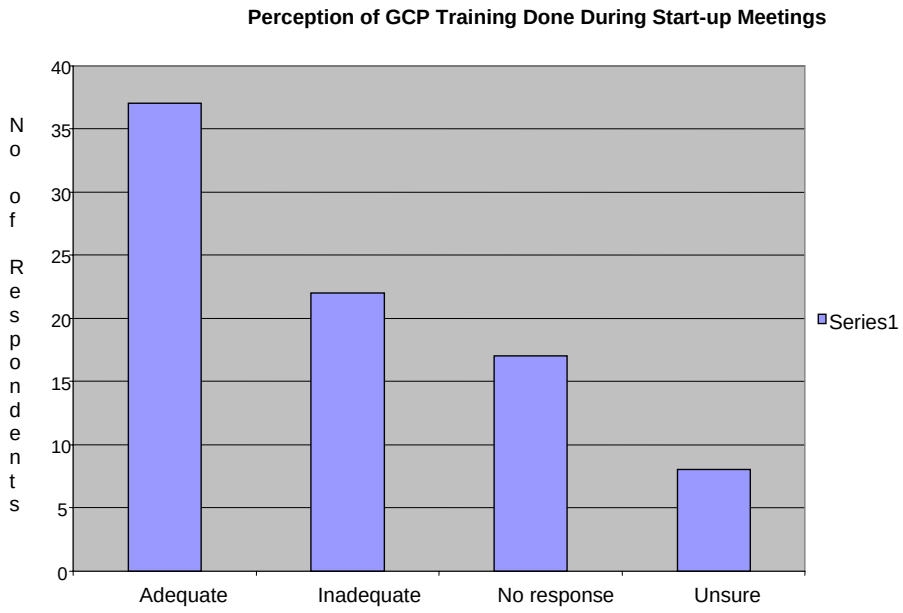
This was followed by the respondents' positive favour of MCC's interest in the number of clinical trials per investigator site (table 5.22d); and the financial disclosure to MCC and Ethics respectively. Both tables showed equal response and same positive attitude of 42.86%.

The least favoured area was the use of placebo in clinical trials, with a positive response of 36.90%. Please refer to table 5.21a.

### 5.3.5.2 GCP Training Given During Start-up Meetings

The participants were asked if the GCP training given during start-up meetings was adequate or not. The response was as per figure 5.7 that follows:

**Figure 5.7 Perceived GCP Training Done During Start-up Meetings:**




Thirty seven percent of respondents felt it was adequate, 22% perceived it as inadequate, 17% did not respond whilst seven respondents were unsure. This shows that the GCP training presented during the start-up meetings should be treated as a refresher activities and be specifically trial related. This training should not replace or overrule the comprehensive formal training needed for all respondents.

#### 5.3.5.3 Factors Affecting Clinical Researchers' Implementation of GCP

The participants were asked about the factors that affect the implementation of GCP. The response is indicated in table 5.23.

**Table 5.23 Factors Affecting Clinical Researchers Implementation of GCP:**

| Factors | No. of Respondents | Percent |
|---|---|---|
| Regular training for staff | 12 | 14.29 |
| Time needed per trial | 4 | 4.76 |
| Experience one has | 1 | 1.19 |
| Cont. readings | 1 | 1.19 |
| No. of studies per site | 1 | 1.19 |
| Resources available | 1 | 1.19 |
| Staff education | 1 | 1.19 |
| No response | 63 | 75 |
| **Total** | **84** | **100.00** |

The above factors reflect issues that affect implementation both positively and negatively. Positive factors include regular training, continuous reading and staff education. Some factors may be both negative and positive, such as if there is adequate time allocated per study, GCP implementation will be good, however, if time is inadequate, implementation may be poor.

The same applies to experience, if having adequate experience, implementation may be good yet if there is inadequate experience, implementation may be poor. As far as the number of studies is concerned; if the studies are few and manageable, GCP implementation may be good; however if the clinical researchers are busy with an excessive number of clinical studies to conduct, GCP implementation may be poor.

The same applies to resources; the fewer the resources, the poorer the implementation possibly whilst the more the resources, the better GCP implementation is likely.

### 5.3.6 Section 6: Experience and Application of GCP

#### 5.3.6.1 Time Spent on Obtaining Informed Consent from Trial Participants/Patients

This was a repeat question. The respondents were asked to indicate the time in minutes that they would spend getting the informed consent from the possible trial participant. This is tabulated in table 5.24 to follow:-

**Table 5.24 Time Spent on Getting the Informed Consent:**

| Time in Minutes | No. of Respondents | Percent |
|---|---|---|
| No response | 23 | 27.38 |
| 5 | 2 | 2.38 |
| 10 | 2 | 2.38 |
| 12.5 | 1 | 1.19 |
| 15 | 5 | 5.95 |
| 20 | 7 | 8.33 |
| 25 | 3 | 3.57 |
| 30 | 22 | 26.19 |
| 45 | 8 | 9.52 |
| 60 | 6 | 7.14 |
| 90 | 2 | 2.38 |
| 120 | 3 | 3.57 |
| **Total** | **84** | **100.00** |

This question was been asked in section 3, question 1. The responses showed that the respondents did not give the same answer, as that given in section three. Apparently, some were not consistent in their response.

### 5.3.6.2 Reasons for Patient Withdrawal from the Study

The participants were asked about the common reasons that contribute to the patients' withdrawal from the clinical trials. The common reasons given were side effects / adverse events and SAE, disease progression, consent withdrawal by patient and other reasons. These will be presented separately in table 5.25 to follow.

**(a) Side effects (SE)/ Adverse events (AE)**

Out of 84 respondents, 37 (44.05%) gave side effects / adverse events as the cause for patients' withdrawal from study, whilst 47 (55.98%) gave no response.

**(b) Disease Progression (DP)**

Ten respondents (11.90%) stated Disease Progression as a cause for patients' withdrawal from the study/clinical trial.

**(c) Consent Withdrawal by Patient**

Nine (10.71%) respondents stated that consent withdrawals by patients, themselves was a reason for withdrawal from study.

**(d) Other Reasons**

The respondents that wrote other as the reasons for withdrawal were asked to specify the "other". This is tabulated in table 5.25

**Table 5.25 Other Causes of Patients' Withdrawal from the Study:**

| Other Reasons | No. of Respondents | Percent |
|---|---|---|
| No response | 65 | 77.38 |
| Pt lost to ff. up | 5 | 5.95 |
| Efficacy lack | 8 | 9.52 |
| Inadequate information | 2 | 2.38 |
| Non-compliance | 1 | 1.19 |
| Relocation | 1 | 1.19 |
| Social reason | 1 | 1.19 |
| Protocol violation | 1 | 1.19 |
| Time limitation | 1 | 1.19 |
| **Total** | **84** | **100.00** |

**Table 5.26 Knowledge of Data Protection Directive:**

| Data Protection Directive Knowledge | No. of Respondents | Percent |
|---|---|---|
| No response | 22 | 26.19 |
| Yes (knowledge of the directive) | 18 | 21.43 |
| No (directive unknown) | 44 | 52.38 |
| **Total** | **84** | **100.00** |

Only 18 (21.4%) respondents claimed to know about this directive. When asked to substantiate their answers, only 2 gave an explanation; the one indicating confidentiality and the other indicating that this should be as per informed consent given.

Twenty-one percent said they knew about the Data Protection Directive, yet only one person indicated a recognised knowledge of this Directive. Similarly, other disparities noted were the fact that the respondents that claimed to know, could not give the details of the directive. Only two respondents were able to give the provisions of the directive.

#### 5.3.6.3 Risks of Participating into the Clinical Trial

The respondents were asked what they told the patients about the risk of participating in a clinical trial. This question was tested and retested (refer annexure 4, section3 question 6c and section 4 question 8) but responses were different.

The respondents were asked to substantiate their responses and specify the risks. Most respondents 72, (88%) did not respond whilst 12, 12 % specified the risk of getting a placebo and side effects. Out of the 12% the breakdown was further done as displayed in table 5.27 below.

**Table 5.27 Side Effects & Placebo as a Risk for Participating in Clinical Trials:**

| Side effects | No. of Respondents | Percent |
|---|---|---|
| No response | 72 | 88.10 |
| Placebo use (chances of falling into a placebo arm) | 3 | 1.19 |
| Side effects | 9 | 10.71 |
| **Total** | **84** | **100.00** |



### 5.3.6.4 The Department of Health GCP Guidelines

The participants were asked if they have read the guidelines published in the Department of Health website (2000). The response is shown in table 5.28a to follow.

**Table 5.28 (a) Respondents Who Have Read the Department of Health Guidelines (2000)**

| SA Guidelines | No. of Respondents | Percent |
|---|---|---|
| No response | 18 | 21.43 |
| Yes | 23 | 27.38 |
| No | 43 | 51.19 |
| **Total** | **84** | **100.00** |

Out of 84 respondents, only 23, (27.38%) have read the South African Guidelines. This response shows a gap in knowledge indicating a training need. The respondents were further asked to identify key provisions of the guidelines. The provisions are listed in table 5.28 (b).

**Table 5.28 (b) Provisions of the SA Department of Health Guidelines (2000) - Specification of Provisions:**

| Specific Provisions | No. of Respondents | Percent |
|---|---|---|
| No response | 78 | 96.43 |
| Quality assurance | 2 | 2.38 |
| Autonomy | 1 | 1.19 |
| Ethics committee | 2 | 2.38 |
| Data management | 1 | 1.19 |
| Subject protection | 1 | 1.19 |
| Best available training | 1 | 1.19 |
| Data collection | 1 | 1.19 |
| Investigator/sponsor Responsibility | 2 | 2.38 |
| Right to withdraw | 1 | 1.19 |
| No jeopardy to care | 1 | 1.19 |
| Subject protection | 2 | 2.38 |
| **Total** | **84** | **100.00** |

The above table 5.28b is a clear indication of clinical investigators' lack of knowledge of the South African Guidelines. Ninenty-six percent of respondents could not give the provisions of the guidelines. This may be an indication that the South African Guidelines are inaccessible, or have not been sufficiently publicised. This needs further research at a later stage.

#### 5.3.6.5 Problems in Application of the Guidelines

The respondents were asked if they had problems in applying the SA guidelines. The response showed that 23 (27.38%) respondents claimed to have read the guidelines and indicated that they had no difficulty in applying the guidelines. One respondent indicated problems with application of the guidelines whilst, 60 did not answer this part. It is possible that some respondents have claimed to have read the guidelines but may not have done so.

#### 5.3.6.6 GCP Course

The respondents were asked if they have attended a GCP course before. A "yes"/ "no" responses was required. After the first response they were asked if they would like to attend one.

**Table 5.29 The Respondents that Have Attended GCP Course Before**

| Done GCP | No of Respondents | Percentage |
|---|---|---|
| No response | 13 | 15.48 |
| Yes | 40 | 47.62 |
| No | 31 | 36.90 |
| **Total** | **84** | **100.00** |

This shows a training need, since almost 37% of respondents have not attended a GCP training course, yet they are involved in conducting clinical trials. It is also possible that those that did not respond, have not done the course which would increase the total to 52%. This is an unacceptable scenario if one needs to ensure patients' safety and quality data.

**(b) Respondents Who are Interested to Attend GCP Course**

Out of 84 respondents 23, (27.38%) indicated that they would like to attend a GCP course, 60 (71.43%) gave no response. This may be an indication that awareness has not been created enough to indicate the lack of knowledge and the implication involved.

**5.3.6.7 Suggested Topics to be Covered by Planned GCP Training Model**

The respondents were asked to suggest the topics to be covered in the GCP course. These are listed in table 5.30 below:-

**Table 5.30 Suggested Topics to be Included in GCP Course:**

| Topics | No. of Respondents | Percent |
|---|---|---|
| No suggestion | 63 | 75.00 |
| SAE handling | 1 | 1.19 |
| All topics | 5 | 5.95 |
| Consent | 1 | 1.19 |
| Consent CRF | 1 | 1.19 |
| Consent taking | 1 | 1.19 |
| Data protection act | 1 | 1.19 |
| Department health GCP | 1 | 1.19 |
| Electronic data capture | 1 | 1.19 |
| Ethics | 1 | 1.19 |
| Evaluation of ICF | 1 | 1.19 |
| GCP training & a register | 1 | 1.19 |
| Handling different patients | 1 | 1.19 |
| Regular GCP update/refresher | 2 | 2.38 |
| SAC medications | 1 | 1.19 |
| Source docs | 1 | 1.19 |
| Training ‘n new dev | 1 | 1.19 |
| Data handling | 1 | 1.19 |
| Finance issues | 1 | 1.19 |
| Study drugs | 1 | 1.19 |
| Study file | 1 | 1.19 |
| **Total** | **84** | **100.00** |

**Table 5.31 Suggestions of What the Sponsor Can Do to Improve the Investigator Conduct of Clinical Trials:**

| Site Improvement | No. of Respondents | Percent |
|---|---|---|
| No response | 73 | 83.08 |
| Reduce paper work | 1 | 1.54 |
| GCP tr. basic & refresher | 1 | 1.54 |
| Continuing education | 1 | 1.54 |
| Formal training | 1 | 1.54 |
| Frequent monitoring | 1 | 1.54 |
| Give reading material | 1 | 1.54 |
| Good quality monitoring | 1 | 1.54 |
| More GCP courses | 1 | 1.54 |
| Quality monitoring & support | 1 | 1.54 |
| Refresher course | 1 | 1.54 |
| Supply copy of SAGCP | 1 | 1.54 |
| **Total** | **84** | **100.00** |

The participants were asked to give suggestions of what the sponsor should do to improve investigator conduct of clinical trials. Out of 84 participants, 73 participants gave no response. The remaining 11 participants gave suggestions as shown on table 5.31 above. This still shows lack of knowledge if not lack of partnership between the clinical investigators and the sponsors. It is important for clinical investigators to know that they need to join hands with the sponsor in ensuring quality data through improvement of GCP knowledge.

### 5.4 Summary of Knowledge Score

The knowledge score was introduced in chapter 4. The following sessions will further look into the expected score versus the score obtained.

#### 5.4.1 The Expected Score

The total expected knowledge score is the total or maximum score that one should have obtained if all the knowledge questions, listed in section 5.4.3; were answered correctly. Each correctly answered question would score a one mark. The maximum score was 17.

#### 5.4.2 Summary of Score Obtained

A global score is presented after combining all knowledge questions as specified in section 3 and 4 of annexure 4 to be further discussed in section 5.4.3.

The 84 respondents were evaluated. The highest score obtained was 15. The mean was 7.9 and the median was 8. This means that fifty percent of respondents obtained less than half of the expected marks. This is the reason that the knowledge gap identified warrants an intervention, which is motivation and training.

One of the previous evaluations in this study examined the relationship between knowledge score and present role in clinical research, please refer to annexure 4, section 1, question 5; ignoring other variables (potential confounding). There is strong evidence of a

relationship with Principal Investigators (PI) and study-co-ordinators scoring much higher on average than co/sub investigators.

The previous multiple logistic regression analysis confirmed these results, showing that adjusting for previous GCP training, being well versed with the Declaration of Helsinki and telling patients about the risks and benefits of the study, co-investigators scored significantly lower (by on average 2.1 marks) than Principal Investigators (PI). This finding is statistically significant. The clinical researcher's role is highly statistical significant as the probability is 0.0000, as shown in table 5.51 (b).

Study co-ordinators scored on average 0.9 marks higher than PI's, but this difference was not statistically significant.

### 5.4.3 Score per Section and by Question

The score per section and by questions is specified below. The sections selected for GCP knowledge are indicated and presented in the subsequent tables. It will further be discussed how scoring was done per section and question:-

**Section 3 Question 2:**

Specific knowledge scenario was discussed in section 5.4.2. and responses given accordingly. The section on GCP Aims was a test re-test question, since this was previously asked.

**Section 3 Question 3: Knowledge of GCP Aims**

**Table 5.32 Patient Safety / Quality Data Knowledge:**

| Patient Safety/Quality Data Knowledge | No. of respondents | Percentage |
|---|---|---|
| Quality Data | 34 | 40.48 |
| Patient Safety | 50 | 59.52 |
| **Total** | **84** | **100.00** |

The expected response from the respondents was the above two which is quality data and patients' safety. The response in the table above shows that the each respondent mentioned one of the above responses as shown in the above table 5.32

**Table 5.33 Other Aims Specified Under Other:**

| Other | No. of Respondents | Percent |
|---|---|---|
| No response/unspecified other | 27 | 32.14 |
| 1 (standardisation) | 21 | 25.00 |
| 2 (ethical issues) | 35 | 41.67 |
| 3 (legal reasons) | 1 | 1.19 |
| **Total** | **84** | **100.00** |

The respondents that had ticked other aim of GCP were asked to specify the other aim. The results in table 5.33 show that 32% respondents could not specify the other aim of GCP and brought the responses uncompleted. 25% indicated standardisation of conduct of clinical trials as the aim of GCP and 41.67% indicated the ethical issues as a reason.

**Section 3 Question 6: Informed Consent Form (ICF)**

**Table 5.34 Inviting Statement Inclusion in ICF:**

| Invitation | No. of Respondents | Percent |
|---|---|---|
| No response | 12 | 14.29 |
| Yes | 53 | 63.10 |
| No | 11 | 13.10 |
| Unsure | 8 | 9.52 |
| **Total** | **84** | **100.00** |

It is a GCP requirement to include an inviting statement to the participant, to ensure that no coercion is done. The above table shows that the majority 53% was compliant and indicated that yes, they would include an invitation to participate to clinical trial, as part of informed consent and information leaflet.

**Table 5.35 (a) Verbal Explanation to Patients**

| Verbal Explanation | No. of Respondents | Percent |
|---|---|---|
| No | 23 | 27.38 |
| Yes | 61 | 72.62 |
| **Total** | **84** | **100.00** |

It is not acceptable to give the potential participant the ICF document without prior verbal explanation, the table 5.35a previously displayed shows that about 27% was non-compliant since they would not give verbal explanation to the potential trial participant.

**Table 5.35 (b) Written IL & Signed IC:**

| Signed Informed Consent | No. of Respondents | Percent |
|---|---|---|
| 0 | 10 | 11.90 |
| 1 | 74 | 88.10 |
| **Total** | **84** | **100.00** |

The majority (88%) in the above table 5.35b were compliant since they would get the written IL and signed IC before any study procedure. This shows compliance with GCP.

**Table 5.35 (c) Written Document to be Obtained for Clinical Trial Participation:**

| Written Document | No. of Respondents | Percent |
|---|---|---|
| 0 (incorrect answer) | 40 | 47.62 |
| 1 (correct answer) | 44 | 52.38 |
| **Total** | **84** | **100.00** |

One of the options given to the respondents listed a signed document as part of things to be obtained prior study participation. This was a deliberately wrong option, given. It is surprising that 44 respondents chose this as an option as indicated in table 5.35c previously displayed.

**Table 5.35 (d) Study Related Procedures:**

| Study Procedures | No. of Respondents | Percent |
|---|---|---|
| 0 (wrong answer) | 52 | 62.65 |
| 1(correct answer) | 31 | 37.35 |
| **Total** | **83** | **100.00** |

The question asked if the researchers would start with a study related procedure, before getting an IC or not. Only 31% got the answer correct, as shown by table 5.55 (d). It is non-compliance to start with a study related procedure before getting the IC. This is violation of human rights and is unethical.

**Table 5.36 (a) Risk:**

| Risk | No. of Respondents | Percent |
|---|---|---|
| 0 (wrong answer) | 14 | 16.87 |
| 1(correct answer) | 69 | 83.13 |
| **Total** | **83** | **100.00** |

The study participants should be told of the risks of participating in a clinical trial, so as to make an informed decision. However 14, 17% clinical researcher (as shown in table 5.36a above), would not tell the potential trial participants about the risks of participating in clinical trials. This is a deviation from GCP requirements and shows lack of knowledge.

**Table 5.36 (b) Specific Risk:**

| Risks specify | No. of Respondent | Percent |
|---|---|---|
| 0 (no response) | 70 | 83.33 |
| Adverse Events | 1 | 1.19 |
| Contact re: problems | 1 | 1.19 |
| For awareness | 1 | 1.19 |
| GCP | 1 | 1.19 |
| Informed decision | 2 | 2.38 |
| Patient to be informed | 1 | 1.19 |
| Patient awareness | 1 | 1.19 |
| Patient's Right | 2 | 2.38 |
| Patients informed consent | 1 | 1.19 |
| Patients informed decision | 1 | 1.19 |
| Side effects | 2 | 2.38 |
| **Total** | **84** | **100.00** |

The respondents were asked to specify the reason for informing the patient about the risks. The table 5.36b above shows the responses.

**Table 5.37 (a) Benefits:**

| Benefits | No. of Respondents | Percent |
|---|---|---|
| 0 (no response) | 12 | 14.29 |
| Yes | 71 | 84.52 |
| No | 1 | 1.19 |
| **Total** | **84** | **100.00** |

The majority, 71 respondents (85%) would specify the benefits. However 12 respondents, 14% did not respond to the question and one that would not tell the risk. This shows lack of knowledge, as shown in table 5.37a above. A follow-up was not made on the reason for non-response.

**Table 5.37 (b) Specific Benefit Reason:**

| Reason | No. of Respondents | Percent |
|---|---|---|
| 0 (no & wrong response) | 79 | 94.05 |
| Advance in research | 1 | 1.19 |
| Holistic healthcare | 1 | 1.19 |
| Proper decision | 1 | 1.19 |
| Proper decision | 1 | 1.19 |
| Understand why trial's done | 1 | 1.19 |
| **Total** | **84** | **100.00** |

The respondents were asked to give specific benefits refer table 5.37b above. The majority, 79 respondents 94% gave no response or wrong answer as a benefit. Only five benefits were specified. This showed lack of knowledge and a training need. This issue needs to be followed up, in future studies.

**Table 5.38 (a) Informed Consent Copy as a Legal Document**

| Legal document | No. of Respondents | Percent |
|---|---|---|
| 0 (incorrect answer) | 54 | 64.29 |
| 1(correct answer) | 30 | 35.71 |
| **Total** | **84** | **100.00** |

The majority of respondents, 54 (64%) did no know that the IC is a legal document as they got the wrong answers, refer table 5.38a. This is of concern since it shows lack of knowledge and should be addressed during the training sessions.

**Table 5.38 (b) IC Copy as a Referral document:**

| Referral document | No. of Respondents | Percent |
|---|---|---|
| 0 (wrong answer) | 49 | 58.33 |
| 1(correct answer) | 35 | 41.67 |
| **Total** | **84** | **100.00** |

The informed consent is used as a referral document where the participants can refer themselves for information such as adverse events, whom to contact in case of problems on the clinical trial. Table 5.38b shown above indicated that only 35, 42% respondents got this correct. This shows knowledge gap and should be addressed by a planned training model.

**Table 5.39 Total Score S3Q6:**

| total score obtained | No. of Respondents | Percent |
|---|---|---|
| 0 | 9 | 10.71 |
| 1 | 2 | 2.38 |
| 2 | 11 | 13.10 |
| 3 | 21 | 25.00 |
| 4 | 27 | 32.14 |
| 5 | 13 | 15.48 |
| 6 | 1 | 1.19 |
| **Total** | **84** | **100.00** |

The above table 5.39 shows the summary of the questions that were used to calculate the total knowledge score. The respondents were expected to score six marks out of this question. The above table shows the respondents that got all answers correct (6/6), that that got 5/6, 4/6 up to 1/6 and wrong answer respectively.

**Section 4:Question 4**

**Table 5.40 (a) CRF Handling:**

| CRF Handling | No. of Respondents | Percent |
|---|---|---|
| 0 | 26 | 30.95 |
| .5 | 4 | 4.76 |
| 1 | 54 | 64.29 |
| **Total** | **84** | **100.00** |

Out of 84 respondents, 54, 64% got the response correct as shown in the table 5.40a above. Four respondents answered the question partially, thus were given half (.5) a mark. For quality data, the respondents are expected to be able to handle CRFs data correctly, using the correct GCP approach.

**Table 5.40 (b) AE Handling:**

| AE Handling | No. of Respondents | Percent |
|---|---|---|
| 0 (incorrect) | 21 | 25.00 |
| 1(correct) | 63 | 75.00 |
| **Total** | **84** | **100.00** |

Table 5. 40b, show that 25% of respondents were unable to handle the adverse events. This is a safety issue and all clinical researchers are expected to be able to handle adverse events.

**Table 5.40 (c) General Knowledge on Section 4:**

| Section 4 score | No. of Respondents | Percent |
|---|---|---|
| 0 (incorrect answer) | 13 | 15.48 |
| 1 | 9 | 10.71 |
| 1.5 | 3 | 3.57 |
| 2 | 15 | 17.86 |
| 2.5 | 1 | 1.19 |
| 3 | 43 | 51.19 |
| **Total** | **84** | **100.00** |

The highest score obtained in this section was 3 which was obtained by 43 respondents, the rest of the responses is as tabulated in table 5.40c. More than 25, 26% respondent got 1.5 and less, including incorrect answers.

### 5.5 Section 4: General Knowledge Score

An overall /global GCP knowledge score was created. In order to calculate the score, the following sections were added:

- Section 3 question 2
- section 3 question 3
- section 3 question 6
- section 4 score

### 5.5.1 Summary of Knowledge Score

**Table 5.41 (a) Total GCP Knowledge Score:**

| Percentiles | Value |
|---|---|
| 1% | 0 |
| 5% | 0 |
| 10% | 2 |
| 25% | 6 |
| 50% | 8 |
| 75% | 10.5 |
| 90% | 13 |
| 95% | 13 |
| 99% | 13 |

The above table 5.41a shows the respondents that scored 0 – 13 marks of the possible 17. This has been broken down into percentiles as indicated above.

**Table 5.41 (b) Knowledge Range Differences**

| Knowledge Range | |
|---|---|
| Observations | 84 |
| Mean | 7.9 |
| Standard Deviation | 3.8 |
| Interquartile Range | 6 - 10.5 |

The interquartile range is the difference between 25th and 75th percentile. In table 5.41 (b) the interquantile range for the 84 respondents ranges between 6 & 10.5, with a standard deviation of 3.8 and a mean of 7.9.

## 5.6 Factors that Influence the Knowledge Score

The factors influencing knowledge that will be examined using the analysis of variance are the following:

- S1Q1: Gender
- S1Q2: Qualifications
- S1Q5: Role
- S2Q1: GCP Training
- S4Q1: Declaration of Helsinki
- S5Q2: GCP training during start-up

### 5.6.1 Gender and Knowledge Score

There is no statistically significant relationship between gender and knowledge score. The data shows that females knew more than the males. However, the difference between males and females is not statistically significant. In addition to this result, one should pay attention to the fact that female respondents out-numbered the male respondents. As a result this picture may not be a true reflection of knowledge differences. This male-female ratio was shown on figure 5.4. This knowledge difference between genders is shown in the following table 5.42a. However, it is difficult to argue the different knowledge levels due to unequal distribution of male and female participants.

**Table 5.42 (a) Gender & Knowledge Score**

| Gender | Mean | Std. Dev. | Frequency |
|---|---|---|---|
| **Males** | 7.45 | 4.02 | 29 |
| **Females** | 8.06 | 3.62 | 55 |
| **Total** | **7.85** | **3.75** | **84** |

**Table 5.42 (b) Analysis of Variance**

| Source | SS | df | MS | F | Prob>F |
|---|---|---|---|---|---|
| **Between Groups** | 7.19019443 | 1 | 7.19019443 | 0.51 | **0.4781** |
| **Within Groups** | 1161.19969 | 82 | 14.1609718 | | |
| **Total** | **1168.38988** | **83** | **14.0769865** | | |

The P- value, given as "Prob > F" in the tables, is the chance of getting such a result if the null hypothesis, of no difference in knowledge score between males and females, is true.

In this case the P-value is 0.4781 equivalent to 47.81%, so this gender result is classified as non-significant since the result is above 0.05.

### 5.6.2 The Effect of GCP Training on Knowledge

**Table 5.43 (a) The Effects of GCP Training on Knowledge**

| GCP Training | Mean | Std. Dev. | No. of Respondents |
|---|---|---|---|
| **Trained** | 8.78 | 2.92 | 58 |
| **Untrained** | 5.77 | 4.55 | 26 |
| **Total** | **7.85** | **3.75** | **84** |

The mean score is higher (8.78 vs 5.77) for those with GCP training.

**Table 5.43 (b) Analysis of Variance**

| Source | SS | df | MS | F | Prob>F |
|---|---|---|---|---|---|
| **Between Groups** | 163.218462 | 1 | 163.218462 | 13.32 | **0.0005 = 0.05%** |
| **Within Groups** | 1005.17142 | 82 | 12.258188 | | |
| **Total** | **1168.38988** | **83** | **14.0769865** | | |

According to Pearsons, in Mateo & Kirkhoff, (1999) the score below 0.05 is statistically significant; and below 0.1% is highly significant. GCP Trained clinical researchers had better knowledge than untrained researchers. The difference in knowledge between the trained and untrained groups is highly significant**,** indicating that GCP training did have an impact on knowledge (Mateo & Kirkhoff, 1999).

### 5.6.3 Qualification and Knowledge Score

**Table 5.44 (a) Qualification & GCP Knowledge Score**

| Qualifications | Mean | Std. Dev. | No. of Respondents |
|---|---|---|---|
| **MBChB** | 5.68 | 4.32 | 17 |
| **Masters** | 7.27 | 4.15 | 20 |
| **Bachelors** | 9.28 | 4.07 | 7 |
| **Other Qualifications** | 8.81 | 2.80 | 40 |
| **Total** | **7.85** | **3.75** | **84** |

**Table 5.44 (b) Analysis of Variance**

| Source | SS | df | MS | F | Prob>F |
|---|---|---|---|---|---|
| **Between Groups** | 138.409471 | 3 | 46.1364904 | 3.58 | **0.0173** |
| **Within Groups** | 1029.98041 | 80 | 12.8747551 | | |
| **Total** | **1168.38988** | **83** | **14.0769865** | | |

The qualification is statistically significant. When one compares the four groups, those with Bachelors Degree scored highest followed by the other qualifications group. Those respondents with MBChB as their highest qualification, scored the lowest of all groups.

When all the groups were compared, it showed a variance of 0.0173, which is less than 0.05 thus statistically significant.

### 5.6.4 Area of Work and Knowledge Score

Here we are looking at those working on private sector versus those in public sector. The analysis will be done individually, that is per sector.

#### 5.6.4.1 Private Sector:

**Table 5.45 (a) Private Practice & GCP Knowledge Score-**

| Private | Mean | Std. Dev. | No. of Respondents |
|---|---|---|---|
| **Not private** | 7.13 | 4.24 | 46 |
| **Private** | 8.72 | 2.88 | 38 |
| **Total** | **7.85** | **3.75** | **84** |

**Table 5.45 (b) Analysis of Variance:**

| Source | SS | df | MS | F | Prob>F |
|---|---|---|---|---|---|
| **Between Groups** | 52.8238054 | 1 | 52.823804 | 3.88 | **0.0522** |
| **Within Groups** | 1115.56608 | 82 | 13.6044643 | | |
| **Total** | **1168.38988** | **83** | **14.0769865** | | |

The above tables 5.45a &b shown little difference between respondents in private and non-private sectors. The analysis shows that there is a marginal score between the clinical researchers on private sector and those that are not on public sector. The difference of 0.0522 shown in table 5.45b, between the groups is not statistically significant.

### 5.6.4.2 Academic Sector

**Table 5.46 (a) Academic Practice & GCP Knowledge Score**

| Academic / Non- academic | Mean | Std. Dev. | No. of Respondents |
|---|---|---|---|
| Non academic | 6.75 | 4.90 | 26 |
| Academic | 8.34 | 3.027 | 58 |
| **Total** | **7.85** | **3.75** | **84** |

**Table 5.46 (b) Analysis of Variance**

| Source | SS | df | MS | F | Prob>F |
|---|---|---|---|---|---|
| Between Groups | 45.6614327 | 1 | 45.6614327 | 3.33 | **0.0715** |
| Within Groups | 1122.72845 | 82 | 13.6918103 | | |
| **Total** | **1168.38988** | **83** | **14.0769865** | | |

This is not statistically significant. Prob>F is 0.0715 as shown in the variance score. The difference between groups on table 5.46a &b is above 0.05 thus not statistically significant.

#### 5.6.4.3 Other Areas of Practice

**Table 5.47 (a) Other Practice & GCP Knowledge Score-**

| Area of Work | Mean | Std. Dev. | No. of Respondents |
|---|---|---|---|
| Provincial Hospital | 6.5 | 0 | 1 |
| Provincial Hospital | 0 | 0 | 1 |
| Provincial Hospital | 0 | 0 | 3 |
| Provincial Hospital | 2.25 | 4.5 | 4 |
| Other Hospitals | 14 | 0 | 1 |
| Military Hospital | 11.5 | .70710678 | 2 |
| Overseas | 7 | 0 | 1 |
| **Total** | **4.5769231** | **5.4842432** | **13** |

**Table 5.47 (b) Analysis of Variance**

| Source | SS | df | MS | F | Prob>F |
|---|---|---|---|---|---|
| Between Groups | 299.673077 | 6 | 49.9455128 | 4.89 | 0.0373 |
| Within Groups | 61.25 | 6 | 10.2083333 | | |
| **Total** | **360.923077** | **12** | **30.0769231** | | |

Other areas of practice mentioned by respondents were provincial hospital (KZN), unspecified hospital & military hospital (Gauteng) and overseas. The knowledge score was evaluated based on the area of practice and score obtained, refer table 5.47a.

The analysis of variance for different hospital respondents (table 5.47b), shows the Prob > F of 0.0373. This is below 0.05 as previously explained in the scoring rate by Pearson, (Mateo & Kirchoff,1999). The score shows statistical significance between the groups in table 5.48.

**Table 5.48 (a) Summary of knowledge score for Provincial Hospital Respondents -**

| Provincial Hospital | Mean | Std. Dev. | No. of Respondents |
|---|---|---|---|
| **No** | 8.51 | 3.01 | 74 |
| **Yes** | 2.95 | 5.08 | 10 |
| **Total** | **7.85** | **3.75** | **84** |

**Table 5.48 (b) Analysis of Variance**

| Source | SS | df | MS | F | Prob>F |
|---|---|---|---|---|---|
| **Between Groups** | 272.68 | 1 | 272.68 | 24.96 | **0.0000** |
| **Within Groups** | 895.71 | 82 | 10.92 | | |
| **Total** | **1168.38988** | **83** | **14.0769865** | | |

Table 5.48 (b) Compares knowledge between provincial hospital respondents and those in both private and public sector practices. The analysis of variance shows a Prob > F of 0.0000 which is below 0.01 or 0.1% .

The difference between groups is then highly statistically significant since it is below 0.1%.

**Table 5.49 (b) Analysis of Variance with Root**

| **Source** | **SS** | **df** | **MS** | **Number of obs = 84**<br>**F(7.76)=11.11** |
|---|---|---|---|---|
| **Model** | 590.861064 | 7 | 84.4087234 | Prob>F =0.0000 |
| **Residual** | 577.528817 | 76 | 7.59906338 | R-squared=0.5057<br>Adj R-squared = 0.4602 |
| **Total** | **1168.38988** | **83** | **14.0769865** | Root MSE = 2.7566 |

#### 5.6.4.4 Summary of Knowledge Score from Question 1-4

The table 5.50 below indicates how the knowledge sore was created. Looking at the summary below one can identify that it is not the whole section that would form the knowledge score but specific questions out of each section contribute to the score.

Section I, does not have knowledge question since it looks more on demographic data, but has elements of demographic data that have an impact on knowledge. These include your place of work, the current role in clinical trials, and your highest qualification to mention but few.

Section 2 Question 1, looks into the trained versus untrained and their knowledge score as previously analysed on table xxx.

Section 4 Question 1, looks into participants that are/not well-versed with the Declaration of Helsinki.

Section 4 Question 8, looks the respondents' knowledge of who is responsible for doing Ethics application according to GCP. The result are then summarised and elements like coefficient, standard error, power and confidence interval looked at. At the end constant trend is looked at for all the groups.

**Table 5.50 Summary of Knowledge Score from Question 1-4**

| Knowsco | Coef. | Std. Err | t | P>\|t\| | [ 95% Coef.Interval ] | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| | 1 | 2 | 3 | 4 | 5 | 6 |
| **Is2q1_2** | -.830998 | .7436836 | -1.12 | 0.267 | -2.312172 | .6501762 |
| **Is1q5_2** | .8674299 | .7637893 | 1.14 | 0.260 | -.6537884 | 2.388648 |
| **Is1q5_3** | -2.145598 | .9415922 | -2.28 | 0.025 | -4.020942 | -.2702546 |
| **Is1q5_4** | -1.276022 | 1.766127 | -0.72 | 0.472 | -4.793568 | 2.241523 |
| **Is4q1_1** | 2.127492 | 1.121323 | 1.90 | 0.062 | -.1058168 | 4.3608 |
| **Is4q1_2** | 2.491049 | 1.058729 | 2.35 | 0.021 | .3824066 | 4.599691 |
| **Is4q8** | 2.991781 | .8193139 | 3.65 | 0.000 | 1.359976 | 4.623586 |
| **Cons** | 4.132304 | 1.164555 | 3.55 | 0.001 | 1.812892 | 6.451716 |

The above table 5.50 shows the summary of all knowledge score obtained by different respondents in each knowledge question as specified above. The subsequent tables will further present the breakdown of knowledge questions in relation to specific categories

like role in clinical research, trained versus untrained, public and private sector participants and knowledge of the Declaration of Helsinki .

### 5.6.5 Role in Research & Knowledge Score

**Table 5.51 (a) Researcher Role & GCP Knowledge Score –**

| Role | Mean | Std. Dev. | No. of Respondents |
|---|---|---|---|
| **Principal inv** | 8.8695652 | 2.7642909 | 23 |
| **Study co-ord.** | 9.2638889 | 2.9628319 | 36 |
| **Sub-inv.** | 4.6363636 | 4.0537514 | 22 |
| **Other groups** | 6.6666667 | 3.2145503 | 3 |
| **Total** | **7.8511905** | **3.751931** | **84** |

Knowledge score was explored in relation to the role of the respondents. Four groups were compared. The study co-ordinators topped the list, followed by the principal investigators. The sub-investigators became the fourth and lowest in the group.

**Table 5.51 (b) Analysis of Variance:**

| Source | SS | DF | MS | F | Prob > F |
|---|---|---|---|---|---|
| **Between groups** | 327.280554 | 3 | 109.093518 | 0.38 | **0.0000** |
| **Within groups** | 841.109327 | 80 | 10.5138666 | | |
| **Total** | **1168.38988** | **83** | **14.0769865** | | |

The clinical researcher's role is highly statistical significant as the probability is 0.0000, as shown in table 5.51 (b) above. This shows difference in knowledge for the four groups as shown in table 5.51a.

### 5.6.6 Declaration of Helsinki & Knowledge Score

**Table 5.52 (a) The Relationship Between Knowledge of Declaration of Helsinki & GCP Knowledge Score**

| S4q1 | Mean | Std. Dev. | No. of Respondents |
|---|---|---|---|
| **No answer** | 3.1923077 | 4.5713713 | 13 |
| **Yes** | 8.875 | 2.6860275 | 40 |
| **No** | 8.483871 | 3.1609172 | 31 |
| **Total** | **7.8511905** | **3.751931** | **84** |

The respondents were asked if they have read the Declaration of Helsinki Further analysis was to establish the knowledge score in relation to who agreed "yes", that they have read the Declaration of Helsinki and those declined by "no" indicating to have not read the Declaration of Helsinki.

**Table 5.52 (b) Analysis of Variance:**

| Source | SS | DF | MS | F | Prob > F |
|---|---|---|---|---|---|
| **Between groups** | 336.503715 | 2 | 168.251857 | 16.38 | 0.0000 |
| **Within groups** | 831.886166 | 81 | 10.2701996 | | |
| **Total** | **1168.38988** | **83** | **14.0769865** | | |

This is highly statistically significant as shown above (table 5.52b) with a probability of 0.0000. Those that knew the Declaration of Helsinki knew better than those that did not know the Helsinki Declaration. The comparison that is measured that showed high statistical significance, is between the two groups.

### 5.6.7 Start-Up Meeting GCP Training & Knowledge Score

**Table 5.53 (a) Start-up Meeting GCP Training & Knowledge Score**

| Start-up meeting GCP | Mean | Std. Dev. | No. of Respondents |
|---|---|---|---|
| **No response** | 4.5 | 4.9371044 | 17 |
| **Adequate** | 8.4054054 | 2.8500435 | 37 |
| **Inadequate** | 9.1590909 | 3.1750004 | 22 |
| **Unsure** | 8.8125 | 1.9628241 | 8 |
| **Total** | **7.8511905** | **3.751931** | **84** |

The respondents had to indicate if the GCP training presented during start-up meeting was perceived as adequate, inadequate or unsure. The table 5.53a show the response of types of respondents. Some respondents (37) perceived the start –up meeting GCP as adequate, others (22) perceived this as inadequate and those (8) respondents who were unsure. The forth category is for those who did not respond. Knowledge score is explored in relation to the four categories.

**Table 5.53 (b) Analysis of Variance:**

| Source | SS | DF | MS | F | Prob > F |
|---|---|---|---|---|---|
| **Between groups** | 247.30903 | 3 | 82.4363434 | 7.16 | 0.0003 |
| **Within groups** | 921.080851 | 80 | 11.5135106 | | |
| **Total** | **1168.38988** | **83** | **14.0769865** | | |

The knowledge between the four groups of respondent is highly statistical significant because it is below 0.01 which is a cut of point recommended by Mateo & Kirchoff (1999). Although those that perceived the start-up meeting GCP as inadequate, appear to have scored more than other group, it may not be a true picture because they outnumber those that have perceived that training as adequate.

### 5.6.8 Reading SA Guidelines & Knowledge Score

**Table 5.54 (a) SA GCP Guidelines and Knowledge Score**

| SA GCP Guidelines | Mean | Std. Dev. | No. of Respondents |
|---|---|---|---|
| No response | 5.6944444 | 5.5443105 | 18 |
| Read SA Guidelines | 8.5 | 2.388419 | 23 |
| not read | 8.4069767 | 3.1381975 | 43 |
| **Total** | **7.8511905** | **3.751931** | **84** |

The above table 5.54a shows the difference between the groups that indicated to have read the SA GCP Guidelines versus those that have not read the SA GCP Guidelines. There is also a third group that did not respond.

**Table 5.54 (b) Analysis of Variance:**

| Source | SS | DF | MS | F | Prob > F |
|---|---|---|---|---|---|
| **Between groups** | 106.69253 | 2 | 53.3462648 | 4.07 | 0.0207 |
| **Within groups** | 1061.69735 | 81 | 13.1073747 | | |
| **Total** | **1168.38988** | **83** | **14.0769865** | | |

The above score show statistical significance. The knowledge between the groups of respondent is significant (below 0.5) but not highly significant since it is above 0.01.

## 5.7 The Methods of Analysis Used to Find Most Important Factors for Knowledge Score

Multiple linear regression models were fitted to find the most important factors in determining the knowledge score, using a backward elimination (stepwise regression) approach.

The variables included in the final model were whether or not the person was trained in GCP, the current role of the respondent and whether or not the respondent was well versed with the Declaration of Helsinki.

**Table 5.55 Analysis of Variance:**

| Source | DF | SS | MS | F F(6.77) | Prob > F |
|---|---|---|---|---|---|
| **Model** | 6 | 489.53 | 81.59 | 9.25 | <0.0001 |
| **Residual** | 77 | 678.85 | 8.82 | | |
| **Total** | **83** | **1168.39** | | | |

**Table 5.56 Summary Table of Regression Analysis:**

| Knowsco | Coef. | Std. Err | t | P>\|t\| | [ 95% Conf.Interval ] | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| | **1** | **2** | **3** | **4** | **5** | **6** |
| a. not tr.in GCP | -.89 | .80 | -1.11 | 0.269 | -2.485594 | .7037559 |
| b. Study .co-ordinators | .66 | .82 | 0.80 | 0.427 | -.9778569 | 2.289051 |
| b. co/sub-inv. | -2.40 | 1.01 | -2.38 | 0.020 | -4.417682 | -.3900109 |
| b. other | -1.85 | 1.89 | -0.97 | 0.333 | -5.620139 | 1.926136 |
| c. yes. Well-versed with Helsinki | 3.85 | 1.09 | 3.52 | 0.001 | 1.672483 | 6.03435 |
| c. no.not well versed with Helsinki | 3.75 | 1.08 | 3.48 | 0.001 | 1.605043 | 5.898359 |
| constant | 5.32 | 1.20 | 4.42 | 0.000 | 2.923995 | 7.72002 |

The reference levels are:

(a) Those trained in GCP.

(b) Principal Investigator.

(c) No response on question of Declaration of Helsinki.

### 5.7.1 Interpretation of Table of Regression: Table 5.56

(a) Those not trained in GCP scored an average of 0.89 lower on knowledge than those trained, but the difference is not statistically significant.

(b) Co-investigators score an average of 2.4 lower than Principal Investigators and this difference is statistically significant.

The study co-ordinators scored higher than co-investigators by 0.66 on average, but this difference is not statistically significant.

The “others” scored lower on average, but there were only three such respondents.

© Those who answered the question on Helsinki, whether they said “yes” or “no”, scored much higher on average than those who did not answer the question.

## 5.8 Conclusion

This chapter has identified the training needs as perceived by the participants and as reflected by their responses. The knowledge score was used as the main determinant of knowledge from the various groups. The factors affecting the knowledge score were examined. In summary, there is an indication of a knowledge gap in all areas of GCP. These include aspects of patient safety and quality data, thus requiring training needs. The areas identified and requested by the respondents will be included in the planned model.

# CHAPTER 6

## DISCUSSION OF FINDINGS

### 6.1 Introduction

The discussion will focus on results from the sections in the questionnaire within the framework of systems theory while some reference will be made to recommendations from key informants and how this will impact on the finalisation of a training model. The criteria for good educational model will be examined and contribute to model development.

### 6.2 Survey of Training Needs in GCP

The survey focused on the following main areas:

- Socio-demographic Data
- Knowledge and application of GCP in conduct of clinical trials for both GCP trained and untrained clinical researchers.
- Patient safety and handling of adverse and serious adverse events.
- Informed Consent
- Data handling, and corrections to Case Report Forms
- Provisions of South African Guidelines in conduct of clinical trials
- Knowledge of Declaration of Helsinki

- Identification of areas and topics perceived by participants as training needs
- Clinical investigators' attitude towards MCC with issues listed below:
  - Supply of medication to patients, after completion of the clinical trial.
  - Placebo controlled trials.
  - Medicines Control Council's (MCC) interest in the number of clinical trials per investigator site.
  - Financial Interest Disclosure to MCC and Ethics Committees.

### 6.2.1 Socio-Demographic Data

This section examined gender, qualification, place of practice and the present role of the participant in clinical trials. Of these, only the level of qualification of the clinical researchers and their present role in clinical trials impacted on knowledge of GCP.

Qualifications*:* The participants with Bachelors' Degree level education had more knowledge than the participants with Masters, PhD and MBChB (see table 5.44a) in respect of the GCP Knowledge item score ($t=0.173$, $p< 0.05$.

The knowledge excess of diplomate nurses was significant, but should be viewed with caution in the light of the large group size.

Moss (1997), however indicates that people with postgraduate training/ qualifications have more insight into their work and training. They perceive training and learning as relevant as possible to their day-to-day professional needs.

Interestingly, highly qualified post-graduates (MBChB) had lower knowledge scores, and may reflect a relatively lower level of experience in this group who scored less.

The present role had an impact on knowledge (see chapter 5, table 5.51a). The study co-ordinators showed the highest knowledge score, followed by principal investigators and the sub-investigators. This probably relates to the fact that study co-ordinators spend proportionately more time on the clinical trial than investigators placing a greater "need to know" burden on them. Put differently, the principles of cognitive dissonance (Wicklund & Brehim, 1976) suggest that information is optimally acquired in response to a stimulus such as a role demand. This is particularly true in conditions that expose a lack of knowledge of competence in a particular task. This imbalance between demand and knowledge create the dissonance and serves as the required stimulus to strive for a greater level of competence. In this setting, it seems likely that the need to perform correctly during clinical trials motivates study co-ordinators to acquire more relevant information with regard to conduct of clinical trials.

GCP Trained participants had significantly higher knowledge score than those that were untrained. This is clearly not an unexpected finding as education is undoubtedly the agent of change (Havelock, 1982). Interestingly, however, participants who perceived GCP training provided at study start-up meetings as adequate, had lower knowledge scores than those who did not.

### 6.2.2 GCP Knowledge and Application

This area focused primarily on GCP knowledge defined as a working knowledge of the Declaration of Helsinki (2000) and the SA Guidelines for conducting Clinical Trials (2000). The application of these principles was tested through clinical scenarios that frequently present themselves in the context of clinical trials.

A lack of knowledge in all domains tested was demonstrated in the respondent groups with and without GCP training, with few respondents achieving scores of greater than 60%, (see table 5.52a & 5.52b; 5.54a & 5.54b). Those that had undergone GCP training, however, fared better than those who had not. This finding supports the notion that regular updates of knowledge are an important component of the ongoing learning process (Davies & Longworth, 1997).

### 6.2.3 Safety Issues

Safety issues explored knowledge of the informed consent elements (for example, need for inclusion of a statement of invitation to participation, informing participants of all risks and potential benefits of the study). Notable deficits in knowledge in this area were found (tables 5.34; 5.35a & b).

Furthermore, when investigators were requested to provide a generic list of risks and benefits of participating in clinical trials, it was not possible for them to do so (tables 5.36 a & b; 37 a & b). This finding is consistent with a similar Spanish study, in which respondents were unable to apply GCP principles to the informed consent process even after a recent training course (Dal-re, 1993).

When asked why respondents were required to furnish trial participants with a copy of the informed consent document, 50% were unsure, only 36% of respondents suggested it might be for legal reasons.

In a final and related question in this area, respondents were questioned as to what the requirements were before a participant could undergo study related procedures. In short, the most alarming finding was that 63% of respondents would execute a trial-related procedure prior to formal enrolment (table 5.35d). The implication of

the findings in this area is that investigators may possess a basic knowledge of the consent procedure, but appear inadequately equipped to apply these principles in the clinical setting. These findings unequivocally highlight this area of need in developing any future training models in GCP.

### 6.2.4 Handling of Adverse Events and Serious Adverse Events

A significant number of respondents (n=21, 25%) appeared unable to manage emergent adverse events in the context of a clinical trial (table 5.40b). In managing serious adverse events, 56 (67%) of respondents were aware of the regulated reporting timeframe.

While this represents a greater level of knowledge than some of the other domains explored, the safety concerns that this result raises in respect of the 33% of respondents who are not familiar with this detail, at the very least represents an urgent and essential training need.

### 6.2.5 Data Handling

In this area, in excess of 50% of respondents were unsure of how to handle data, correct data entry errors in the CRF, from which a further training need is clearly defined (table 5.15).

### 6.2.6 Attitude Section

Respondents were asked for their views on points over which disputes frequently arise in the clinical trial industry. These include :

- Financial interest disclosure to MCC and Ethics Committees: Here the majority of respondents felt positively disposed to financial disclosure to regulatory and ethics bodies for reasons of transparency (42%%). Interestingly, a differential response to this item was noted with a preference for disclosure to ethics committees. Of the remaining respondents, 48% chose not to respond to this item and only 8% felt negatively about this matter (table 5.22). Lo, et. al, (2000) have suggested that investigators easily feel that conflicts of interest may occur in a setting where clinical trials compete for clinical and pure research time, while competing studies from other firms may also compound the difficulty in this area.

- Placebo-controlled trials: the minority of respondents (37%) felt positively about the use of placebo-controlled trials (refer to table 5.22b). However the respondents did not specify the reason behind such a response, this is the area for further research in future.

- Supply of medication post trial: 57% of respondents support the idea of an ongoing supply of medication upon study completion, if the clinical response was adequate. The same group regarded the matter as the responsibility of the company (table 5.22c).

- Regulatory authority (MCC) interest in the number of studies each site is conducting was viewed positively in only 43% of respondents (table 5.22d). In addition, respondents felt that in the interests of generating high quality data, the number of studies per site should be limited. A small majority of respondents (54%) chose not respond to this, making meaningful comparison in this area impossible.

### 6.2.7 Training Needs as Perceived by the Participants

This section required an indication of the areas felt to be in particular need of refreshing knowledge through training updates. Specific areas of need included, source data verification, investigator responsibilities, study agreements, patient safety, quality assurance and data handling. 47% of respondents indicated that they needed training in all areas that were listed in annexure 4, section 2–question 4.

Other areas (table 5.30) requiring training needs included an approach to FDA audits, time management, electronic data entry and SA GCP Guidelines. These should form part of the training model components.

### 6.2.8 The Provisions of the Declaration of Helsinki & SA Guidelines

In respect of knowledge of the Declaration of Helsinki (2000), 40 respondents indicated that they were well versed, but when asked to

specify some of the detail therein contained, no detail was provided. The additional training in the knowledge of the Declaration of Helsinki forms an important provision of the SA guidelines. Similarly alarming results were demonstrated when enquiring about the South African guidelines. Only six respondents could specify at least one provision of the guidelines. From this, it seems unsurprisingly that the participants themselves cannot always recognize the need for further knowledge and training. It has been shown that people are only sensitized to the need for training in a specific area when they fail to respond to specific knowledge related question (Jones & Mann, 1992 & Wicklund & Brehim, 1976).

### 6.2.9 Reasons for patient withdrawal from the study

Respondents were asked about the reasons patients withdraw prematurely from the study. Respondents suggested side-effects (44%), disease progression (12%) and consent withdrawal (11%) were the most frequent reason for premature participant withdrawal from clinical trials (see 5.3.6.2 a-c).

Less frequently encountered reasons included being lost to follow-up, inadequate information, relocation of subjects, social reasons, non-compliance and lack of efficacy. The above responses showed a knowledge gap for the respondents.

### 6.2.10 Suggested Topics to be Included in the Proposed Training Model

When asked to give suggestions on the topics to be included in the proposed training model, sixty-three participants gave no suggestions whilst twenty-one respondents suggested topics including informed consent process, source data verification, data handling, investigator responsibilities, study agreements, patient safety, quality assurance, handling of study drugs; electronic data capturing; writing source documents; GCP updates and finally information on the Data Protection Act.

### 6.2.11 What Should the Sponsor Do to Improve Conduct of Clinical Trials

Respondents indicated that they felt paperwork should be reduced and that continued involvement in GCP training (basic and refresher courses), frequent monitoring, providing continuous support and supplying sites with SA Guidelines for clinical trials, was of priority.

## 6.3 Conclusion

This chapter has summarised and discussed the study findings including areas that reflect knowledge gaps or training needs in relation the questionnaire responses and is in line with literature discussed in chapter three. Knowledge-based items clearly showed that intervention is required to increase the levels of GCP knowledge and address the identified needs of the clinical researchers. These areas form the basis from which the training model is developed.

# CHAPTER 7

## PROPOSED GCP TRAINING MODEL

### 7.1 Introduction

The proposed model that will be presented below is based on the findings of a survey of training needs of clinical researchers, literature related to the conduct of clinical trials and to ideal training models (Edwards & Talbert, 1999). Further input was obtained from the report on the recommendations from the key informants discussed in chapter 4 section 4.3.5. Criteria for good educational models were used as basis for the model development (National Governors Association, 2003; Nijhof & Streumer, 1998).

The model seeks to be flexible (Roberts-DeGennaro, 1993), which implies use by novices as well as more advanced clinical researchers for whom an update on knowledge is necessary. The time to be spent undergoing training will depend on resources and the level of experience for the group that is being trained (Bailey, McWilliams, & Winton, 1992).

During training sessions the researcher supports the proposal that trainees should be grouped according to the level of experience (Nijhof & Streumer, 1998). Further, we propose that for each training session, a mini survey of training needs should be undertaken (see

figure 7.1 (Murk, et. al., 2000; Robert-DeGenaro, 1993). This will sensitise the trainer to the areas of particular interest or knowledge deficits in the particular group. Sessions should close with an evaluation and assessment of learning in the particular session. This does not replace a follow-up evaluation and feedback that should done after five to six months (Robert-DeGenaro, 1993). Guidelines recognize the need to move information around within a course to accommodate participants, but stress achieving the end goal of improved knowledge and confidence to practice within a GCP model.

The model herein proposed that the model can be adjusted meet the specific needs of the potential trainees, based on the outcome of the mini-survey that should precede every training session planned.

## 7.2. The Proposed Model

The proposed model is divided into sections (figure 7.1). In this figure, system components (outcomes, input, process / throughput, learning areas in outcome based education (OBE) principles) are represented schematically and discussed individually below:-

### 7.2.1 The Learning Outcomes of the Proposed Model

The outcomes of the model are clearly stated to ensure that at the end of training, the trainees are able to synthesize GCP knowledge and attitude with practice. Indeed, the application of GCP principles

form the foundations for assessment criteria, to be used to ensure that learning has taken place.

1. Clinical researchers should be able to apply GCP Principles in the conduct of clinical trials from the planning to the completion phases of the clinical trial (Department of Health, 2000: requirements for all clinical researchers).

2. Clinical researchers should be able to ensure patient safety by correct reporting of adverse events and serious adverse events (Raven, 1993; and the results of the survey of training needs).

3. Clinical researchers should demonstrate the ability to execute crucial clinical trial related procedures that include, but are not limited to obtaining informed consent from participants.

4. The clinical researcher should be able to communicate clearly with trial participants, relatives and other researchers involved in the study.

5. Clinical researchers should demonstrate the ability to perform the correct and safe methods of handling the clinical trial drugs. It is important to be able to demonstrate knowledge and experience of the procedures including drug storage, dispensing and accountability throughout the conduct of a clinical trial (Department of Health, 2000; MRC, 1998; standard requirements).

6. Clinical researchers should demonstrate the ability to correctly and accurately enter data from source document to case report

forms (CRF) or electronic CRF depending on the study being conducted (Department of Health, 2000; ICH GCP, 1996)

7. Clinical researchers should possess the necessary problem-solving skills to manage trial related eventualities.

8. The clinical researcher should be able to enter data accurately and timeously in CRF, this includes both manual and electronic data entry

9. Researchers should be able to successfully submit proposed studies to relevant ethics and regulatory authorities to seek approval for the proposed site.

10. Clinical researchers should be able to prepare for an audit in a clinical research setting and able to demonstrate documents in place, including the DOs and DON'Ts of the clinical trial

11. Clinical researchers should be able to identify, communicate and implement the key issues in the South African Guidelines in Conducting Clinical Trials (Department of Health, 2000; training needs survey result).

### 7.2.2 The Proposed GCP Training Model

#### 7.2.2.1 Outcomes

The desired outcomes are to ensure that upon completion of the training course, trainees are able to synthesize GCP knowledge and attitude with practice. The result will be that investigators feel more comfortable with respect to being able to apply the GCP principles,

ensuring patient safety, following correct procedure in obtaining informed consent, demonstrating ability to communicate clearly and successfully with the patients, relatives and fellow researchers. Secondary benefits include development of problem solving skill and closer attention to accurate data-handling and managing MCC and ethics applications (Norman, 1988).

#### 7.2.2.2 Input

This is the driving force of the training model. It is the source of energy and guidelines for the model. Through the input from the literature on development of the training model; information from the key informants as indicated in figure 7.1, towards the end of this chapter, requirements of OBE and amalgamation of adult education principles, results of the survey of clinical researchers' training needs, one is able to determine the outcomes and areas of learning. This is the reason the input is looked upon as a driving force for the whole model.

#### 7.2.2.3 Process / Throughput

Adult education principles and Outcomes Based Education form a vehicle for compiling (context), the mode of delivery (application) of the training model. The vehicle (training model) will be influenced by results from the mini-survey conducted at the start of training

sessions as well as the level of GCP knowledge of participants (Department of Education, 1997).

#### 7.2.2.4 Output / Outcome

Using the learner-facilitator approach, the proposed model should achieve the goals of being a good GCP training model. Training using this model will then go a long way to ensuring that researchers are competent clinical trial investigators that are then more likely to produce analyzable and credible data.

The proposed model will be used in conjunction with the Outcome Based Education Approach and Adult Education Principles. Stuffelbeam (1971) uses the systems approach in the evaluation of educational models. The context and input are understood and have their basis in a more global view of the systems approach (Gillies, 1994). In figure 7.1, arrows linking the process, which are the vehicles with which to achieve specific outcomes (product, according to Gillies), allows the bi-directional flow of information, with feedback for reshaping aspects of the model. The need to use both approaches is to ensure that whilst change is being introduced in certain aspects / units of the global system of clinical trials conduct, other systems are able to adjust and reshape in order to reach a common goal, best clinical practice levels of care.

#### 7.2.2.5 The Outcome Based Education and Learning Areas

Outcome Based Education (OBE) reflects the paradigm shift from the traditional teaching approach to a learner-centred approach. The learner is viewed as a complete unit and not an empty vessel. It focuses on what the learner knows and can achieve and on the success and not failure (Department of Education, 1997).

The main objective is to help the learner succeed by testing knowledge and skills simultaneously (Department of Education, 1997; Educators in Connecticut's School District 15, 1996). Assessment of participants will be continuous during the model delivery, even after every session completed. It is recommended that after five to six months there should be assessment and evaluation following completion of the course.

### 7.2.3 The Educator

In the OBE model, the educator functions as a facilitator who guides students in learning versus the traditional approach in which the teacher was there to prescribe what should be learnt. The educator's characteristics include demonstration of efficiency, reading and going beyond the student knowledge. The educator looks at what the learner knows and can do

### 7.2.4 The Three Areas of Focus

In OBE, three areas need to be focused by the educator in order to ensure that learning takes place. Knowledge of these areas ensures proper planning and implementation of all educational sessions. These focus areas include learning, assessment and outcomes areas (Department of Education, 1997).

#### 7.2.4.1 Learning Areas

The learning areas are the components of GCP that have been identified as areas in which training is needed and thus define the basis for the outcomes. These include communication, problem solving skills, organization/management of the practice, as well as collecting, organizing, analyzing and critically evaluating trial information. The final model will be set within the systems approach to address all of these identified areas.

#### 7.2.4.2 Assessment Areas

OBE proposes a continuous approach to assessment that incorporates assessment of skill, knowledge, attitude and values or SKAV. Assessments may take the form of group projects, interviews and oral presentations, written and peer assessments, practical

assessments and learner portfolio assessment (Department of Education, 1997).

#### 7.2.4.3 Outcome Areas

The outcome areas refer to areas or domains in which the learner is able to demonstrate knowledge of strategies that they can use to achieve learning goals. Outcomes include seven critical cross-field areas as shown in table 7.1. The outcome areas planned should indicate that:

a. The learner can communicate

b. They possess problem solving skills

c. Life skills knowledge

d. Organization and analytic thinking

e. Organization and critical evaluation

f. Understanding that the world is made of the set of related systems

g. Use of science and showing of response towards environment and health of others.

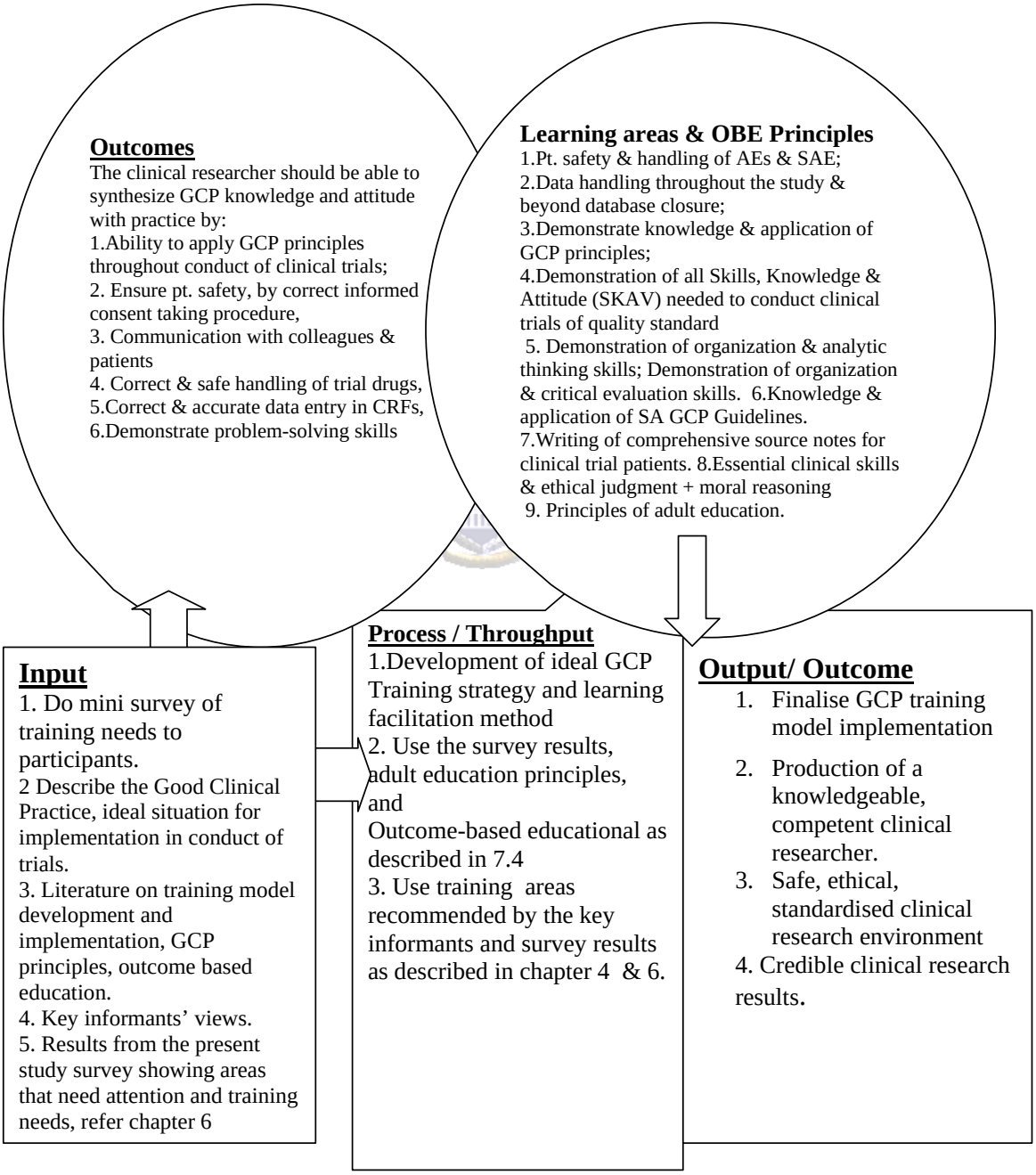
The above-stated outcome areas are in line with the principles of adult education which stipulate that an adult is self-directed, has experience, has motivation to learn and is ready because of the value she / he puts on need for learning (Knowles, 1984).

In order to be able to apply this approach, one should be able to differentiate between the two methods of teaching, the traditional versus the outcomes Based approach (Department of Education, 1997; Educators in Connecticut's School District 15, 1996) shown in table 7.1.

**Table 7.1: Traditional versus Outcome Based Education (OBE) – (Department of Education, 1997)**

| Traditional Approach | Outcomes Based Education Approach |
|---|---|
| 1. Content-based | 1. Outcomes-based |
| 2. Passive learner | 2. Active learner |
| 3. Rout learning | 3. Critical thinking |
| 4. Systems, content based, information is broken down and given to subjects | 4. Integration of knowledge, learning is relevant to the real situation of learners which are complete units with prior knowledge and experience |
| 5.Text-book and worksheet based teaching approach | 5. Learner centered, teacher is a facilitator, use of group-work and variety of sources |
| 6. The teacher is responsible for learning, motivation depends on teacher personality | 6. The learner takes responsibility for learning, the learner is motivated by constant feedback and affirmation |
| 7. Teacher dictates to the learners | 7. The educator adapts to the learner strategies |

**Figure 7.1: The GCP Proposed Training Model**



### 7.3 Pre-testing the Model

Pre-testing the model is beyond the scope of the present study, but is essential that this process be carried out in the next phase of the study in order to validate the model.

However, the researcher has solicited the views of the panel of key informants and this input will be used to finalize the proposed model.

### 7.4 Training Approach

The training approach in adult education within the confines of an outcome based model (Department of Education, 1997; Educators in Connecticut's School District 15, 1996), is recommended to be largely participatory.

## 7.5 Conclusion

This discussion chapter has dealt with development of a proposed training model using an outcomes based educational model. The systems approach continued to provide an umbrella under which this approach was taken.

Educators using the proposed model, following future validation, will continue a process of development as they interact with the model in the process/throughput phase, and will be in the position to effect further change based on emergent gaps in participant knowledge base. Assessment is an integral part of all phases of the model.

The next chapter will deal with the results of the key informants review and recommendations for the proposed model and then present the final model.

# CHAPTER 8

Comment [HNU2]: Nomusa, please be cautious about this chapter as I have edited it in many stages and may have lost the flow

Comment [HNU1]:

## THE FINAL GCP TRAINING MODEL

### 8.1 Introduction

The final model that will be presented below represents the product or final output of this thesis.

The organization of this study has been guided by systems theory. To establish a model for training n GCP, the researcher has (1) sought input from key informants in the area of GCP to inform the initial composition of the survey questionnaire, (2) piloted the proposed questionnaire after which adjustments were made, and (3) surveyed clinical researchers' knowledge base and training needs using the developed instrument.

The model we now present represents the synthesis of the findings form the survey above and the final inputs from key informants, and is based on criteria for a good educational model (National Governors Association, 2003; Nijhof & Streumer, 1998).

## 8.2 The Key Informants Recommendations

Of the original panel of 5 key informants, 2 were available to critically review the proposed model. Independently of one another, both key informants supported the model in its present form, and confirmed that the content accurately reflects their original inputs, in respect of training needs for the clinical researchers. The recommendations for the finalisation of the model were as follows:

### 8.2.1 Training Sessions Division For Two Groups

Key informants recommendations were that the training sessions divide trainee groups into clinical trialists and study co-ordinators. This will allow more specific training in the areas that form the main focus of each of these groups' roles in clinical trials. Grouping in training sessions, was proposed in addition to the division proposed by the researcher of separating groups on the basis of trial experience and previous training. Implementation of these divisions will be based on the mini-survey proposed for the start of all training sessions.

### 8.2.2 Limitations for the Training Model

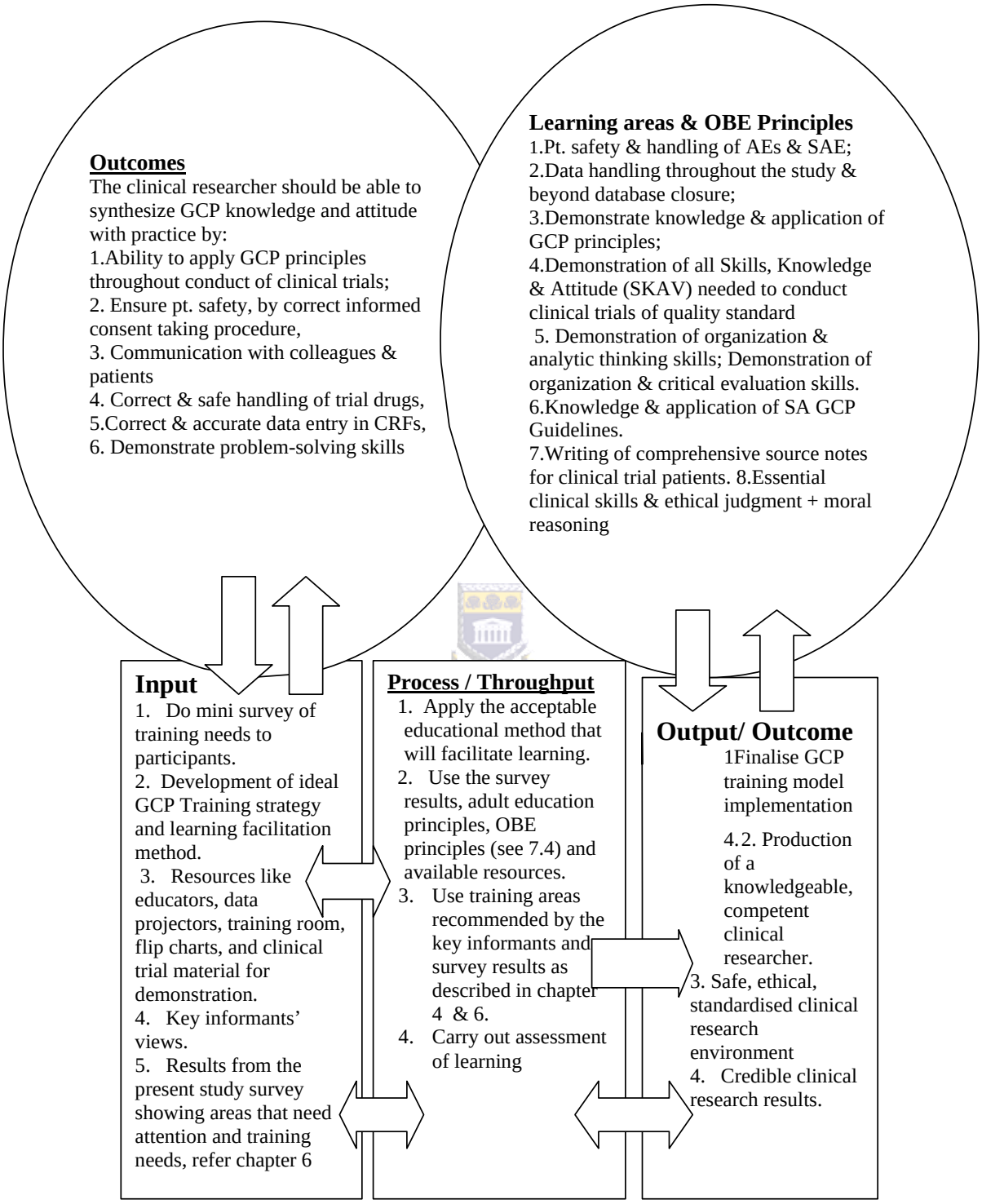
It was noted that the version reviewed by the key informants did not contain a section describing the resources needed to implement the training model. In addition, it was pointed out that the final model should incorporate a section on the potential and known limitations of the model.

The researcher had purposefully avoided specification of required resources, as she felt that prospective educators were better placed to make these decisions based on information received through the mini-survey conducted at the beginning of training sessions. While on the one hand this would necessitate the conducting of mini-surveys prior to the training session day, the principle is strongly embedded in the flexible nature of the systems theory adopted here. On balance, the researcher has elected to include a list of resources that will be required on the basis that this list is neither exhaustive of rigidly prescriptive.

### 8.2.3 Continuous Review, Updates and New Versions

An important consideration of training models is their innate ability to remain abreast of the most recent developments in the field of study. The advantage of a flexible model, is that it permits users to inputs new developments as they become available. If fundamental changes occur, fully revised an updated model versions may be necessitated. It is also likely that if the results of the mini-surveys are consistent across sessions, that these may represent a second stream of inputs to the updating process.

**Figure 8.1: The Final GCP Training Model**



## 8.3 The Relationship of the Components of the Model

In keeping with a systems approach, interrelated sub-systems remain able to function independently, yet a degree of interdependency exists by virtue of the strength that the function of communication brings to the system as a whole. Each sub-system comprises the following components:

### 8.3.1 The Input

Input, the driving force of the training model requires energy and provides the development guidelines for the model. Inputs from literature, key informant survey, clinical researchers' survey of training needs have been combined with the principles of OBE and other contemporary adult education principles to define the desired outcomes and areas of learning (figure 8.1).

### 8.3.2 The Outcomes

The derived outcomes define the level of knowledge in GCP trainees should have upon completion of the training model. Whether or not these outcomes are achieved is amenable to objective testing.

### 8.3.3 The Throughput / Process

The throughput constitutes a number of essential processes required for developing an optimal learning facilitation method in

pursuit of the desired outcomes. Principles in adult education in conjunction with an outcome based educational model will be used as vehicles for compiling (context) the mode of delivery (application) of the training model ( Arndt & Huckabay, 1980).

### 8.3.4 The Learning Areas and OBE Principles

Outcome Based Education (OBE) represents a move from traditional education models to a more learner-centered approach. This model views the learner as a complete unit and not as an empty vessel. A such the focus is on creating an awareness of what the learner knows and what can be achieved all of which brings success, with careful attention not to focus on failure. The focus is on the succeeding learner, while opportunities to test knowledge and skills simultaneously (Department of Education, 1997; Educators in Connecticut's School District 15, 1996). The proposed model, assessment and evaluation of participants will be continuous during the model delivery for an example after every session completed. It is then recommended (Dept. of Education, 1997) that after five to six months there should be assessment and evaluation following completion of the course. This will ensure re-training if the gap is identified or the giving of refresher courses. These refresher courses may be given to reinforce the knowledge or give new information that has erupted after completion of training.

### 8.3.5 The Output / Outcome

The end goal of this process remains the development of a validated educational model in GCP, that when implemented, will be effective at equipping clinical trial investigators to competently participate in clinical rug trials. Furthermore, the model will create an environment within which to conduct clinical trials, which will produce trial data that are credible.

The proposed model will be used in conjunction with the Outcome Based Education Approach and Adult Education Principles. The context and input should be made to fit into the global Gillies, (1994) systems approach. The process, (throughput, according to Gillies) is the vehicle used in order to achieve the specific outcome (also called product, according to Gillies). The need for using both approaches is to ensure that whilst change is being introduced on certain aspects / units of the global system of clinical trials conduct, other systems are able to adjust and reshape in order to reach a common goal aiming at achieving the best practice.

This is achieved through the use of the ideal training model that is based on literature, key informants input, adult education principles, outcome based education the results of the training needs survey and standard requirements for the competent clinical

researcher (Department of Health, 2000; Department of Education, 1997).

### 8.3.6 The Linking Arrows: Relationship of Components of the Model

One of the characteristics of the systems theory is the fact that the sub-systems or unit are able to communicate with each other (Gillies, 1994; Arndt & Huckabay, 1980;). This flow of information (represented by the arrows) between sub-systems is crucial to effective running of the whole. The arrows in this diagram form linkage within the sub-systems. The flow of information remains a function of the interdependency of sub-systems. In particular, the link between input and output apparently bypassing the throughput phase, highlights the importance of knowledge of the outcomes when input variables are considered. This process gives educators a measure from which to evaluate candidates as they progress through the programme. The outcomes also refer to the more global targets, which are not purely GCP, however mastery of these areas, have significant impacts on the context in which GCP is practiced.

**Arrow to the left circle:** This arrow ensures communication during the process or training implementation phase. The communication during implementation phase ensures that during

learning facilitation procedures, principles as outlined above are borne in mind. This ensures that the delivery method remains true to the model by covering all the necessary learner areas. Evaluation remains a key facet of delivery and should be in line with what knowledge the model has offered.

**Arrows from the left circle and throughput to the output/outcome:** Both arrows feed the output simultaneously to indicate interrelatedness of the components whilst at the same time indicating the flexibility of the system, allowing flow of information simultaneously from sub-system to the other This is necessary in a sense that the product is dependant on the throughput, indicating the kind of learning that has taken place. At the same time it is important at the output phase to measure the results, against the elements of the learning areas, using the OBE principles (National Governors Association, 2003; Department of Education, 1997).

Bi-directional arrows: Represents the multidirectional communication between all levels of the system to ensure effectiveness and sustainability. Educator learning facilitation happens in part continuous assessment, through which re-training and reshaping to help realise the final goal. Summative evaluation, will also lead to the repeat of the cycle maybe at an advanced level or using the revised version based on the new results and new information on GCP and on the conduct of clinical trials which may

be country specific or international requirement (Department of Education, 1997; Gillies, 1994).

### 8.4 Justification of a Finalised Model

The final model derived form this study continues to meet criteria for an ideal model in that it has a:-

#### 8.4.1 Clearly Stated Purpose

This is clearly stated (Fig 8.1). By implication, GCP training, properly implemented, will produce competent clinical researchers.

#### 8.4.2 Clarity



This model is clear both in general appearance (which is what) its content and outcomes. Examination of the individual components shows that these are clearly identifiable, and that communication between them is ongoing.

#### 8.4.3 Flexibility

The proposed model is for use in a number of settings by people of varied training backgrounds.

#### 8.4.4 Specificity

The proposed model leaves one in little doubt that this is a GCP training model. The flexibility inherent in the system, however, may

allow you to introduce new designs in keeping with changes to the training fellowship

### 8.4.5 Scientific

Scientific rigor, has been ensured in all phases of the study from the earliest stages of development to the completion involving the final input from the key informants on the development of the final training model. There have been no deviations from the planned methodology, with the exception that the designed model could not be pre-tested in the field.

### 8.4.6 Adaptability

The strength of this model is its inherent adaptability provided adequate information is gathered prior to implementation of changes for a particular situation or group of trainees.

### 8.4.7 Unique yet Innovative

This training model represents an original development with particular application to the South Africa context. The researcher has successfully shown that specific needs exist in the South African context, and with the input of a group of representative key informants, has developed this innovative model that incorporates all the essential elements of GCP required to equip investigators to conduct clinical trials in compliance with available guidelines.

### 8.4. 8 Worthy and has Expected Benefits

This training model is worthy and has expected benefits. It is worthy in that it is the first known training model in the country that is scientifically based. It has incorporated both local and international GCP requirements. It has expected benefits in that during its application, the users will be able to further evaluate it and made further modifications. It will be usable over a long period of time whilst at the same time being made adaptable to any situation (National Governors Association, 2003; Nijhof & Streumer, 1998; Meleis, 1985).



### 8.4.9 Predictability

If correctly administered, all the indications point to the fact that the model will successfully increase levels of GCP knowledge in trainees. While this can only be unequivocally stated once field-tested, the learning areas on which the model has concentrated, are derived specifically from the areas in which knowledge was shown to be deficient in the survey conducted in the present study. Finally the requirement of continuous evaluation, will permit specific area of deficient knowledge to be identified and corrected timeously.

### 8.4.11 Conceptual Base

The systems approach used, shows the various stages that include the input, whereby the information is gathered to develop the model. The next stage is the process then the final stage is the output.

At this point, model is in a process stage, but during implementation phase, it has a potential of developing to become a conceptual model. This will be achieved by the people who will be using it, who will be able to identify it's strong points and limitations. The model will be revised as new information comes up and new developments arise. There will be new versions that will be made available from time to time. Application will enable the chances of modifications depending on what has been identified. Through continuous use, the present model will be end up being a conceptual model and at a later stage after continuous use may end up being a theoretical model (National Governors Association, 2003; Nijhof & Streumer, 1998; Meleis, 1985).

## 8.5 Conclusion

This chapter dealt with a final training model. This model has been discussed and justified to indicate that it meets the criteria for a model. It can be evaluated using the principles or criteria for model / theory evaluation. It is believed that after continuous use, this will show the contribution it will add to the scientific knowledge. For further research, it is recommended that the same study be conducted, with modifications of the research instrument, taking into consideration the study limitations highlighted in chapter 4 and the model limitations discussed in this chapter. This will further allow modifications and development of further models or versions.

# CHAPTER 9

## CONCLUSION AND RECOMMENDATIONS

### 9.1 Introduction

The GCP training model designed and presented in this thesis represents an important step in the development of a validated model for use in South Africa. Furthermore, it represents a significant start in the development of much needed standardized and accredited training programmes in GCP with which to equip staff involved in clinical trials in the South African context. The present model is compliant with all contemporary GCP guidelines and incorporates information related to particular areas of concern in respect of GCP knowledge in this environment.

While the study is to some extent limited by the fact that validation of the final model in the field has not fallen within the scope of the present thesis, a valuable process of ongoing development has been initiated herewith, with the result that such validation will not be unnecessarily delayed. The model is advantaged by the systems approach taken in development. Flexibility and adaptability to specific needs are particular advantages of the proposed model.

## 9.2 Implementation of the Final GCP Training Model

The finalized model has not been implemented or, although it has been reviewed by the key informants before finalisation. Since this is a limitation for the study, it is however recommended that this model be applied in future so as to allow evaluation during and after implementation. This will help in discovering the unknown weaknesses and strength of the model thus help in re-shaping of the model and or further development of new theories.

## 9.3 Mini-Survey to Precede GCP Training

The process of ongoing development referred to above will require that the mini survey of training needs proposed before the start of all training sessions. This will ensure that new GCP training needs that were not identified during the present model development, will be identified at this point.

## 9.4 Continuous Review of the GCP Training Model

Apart from implementation, experts will be requested to review the developed model on regular bases. This will ensure that it maintains its contemporary appeal in GCP training (Dale, 1993).

## 9.5 Recommended Areas of Research

The study examined the levels of training, the nature of previous training as well as the specific training needs of a sample of clinical trial research staff in a South African context. Future research should probably also evaluate course content of previous training in order to assess whether inadequate or ineffective training is the cause for knowledge deficits.

Further area of research is on the accessibility and the use of the South African GCP Guidelines. This was triggered by the lack of knowledge of the guidelines. It is unknown whether lack of knowledge is due to inaccessibility of the guidelines or lack of distribution.

## 9.6 Refresher Courses and Updates

Loss of GCP knowledge, even if previously trained combined with the dynamic development of GCP guidelines, highlight the need for refresher courses and regular GCP updates (Davies & Longworth 1997).

## 9.7 Conclusion

The study has realised all three primary objectives including: (1) the development of the research tool for use in a survey of training needs in GCP, (2) to conduct a survey of training needs and (3) to develop a GCP training model, based on the findings of the survey and inputs from key informants that is now ready for final filed testing and validation.

## 10. The List of References


Academy Search Premier. (1997). *Training models: Summary. Physicians- education (continuing education)*. Canada. Vol. 20. (4): p. 262-264.

American Psychological Association. (1994). *Publication Manual of American Psychological Association.* 4th Edition. Washington, DC: American Psychological Association

Anderson, A. H. (1992). *Successful training practice: a manager's guide to personnel development.* United Kingdom: Blackwell Publishers.

Armstrong, D. & Grace, J. (1994). *Research methods and audits in general practice*. Oxford: Oxford University Press.

Arndt, C. & Huckabay, L. C. D. (1980). *Nursing administration: theory for practice with a systems approach*. London: The C.V. Mosby Company Publishers.

Ausubel, D.P. (1967). *Learning theory and classroom practice*. Toronto: Ontario Institute for Studies in Education.

Bailey, C., McWilliam, N. & Winton, M. (1992). *A guide to field research.* United Kingdom: Pine Forge Press.

Bakana, W. H. (1971). *Training in depth interviewing.* New York: Harper and Row Publishers.

Batty, C.; Jette, D. U.; Bacon, K.; et. al. (2003). Evidence-Based Practice: beliefs, Attitudes, Knowledge, and Behaviours of Physical Therapists. *Physical Therapy*. Vol. 83 (9) p. 786 - 805.

Beard, R. M., & Hartley, J. (1984). *Teaching and learning in higher education***.** 4th Edition**.** London: Chapman Publishers.

Bell, J. (1989). *Doing your research project: A guide for first-time researchers in education and social science*. Philadelphia: Open University Press

Bloom, B. S. (1954). *Taxonomy of educational objectives: The cognitive domain*. New York: McKay Publishers.

Booth, A. (1995). *The Craft of Research*. Chicago: University of Chicago Press.

Bossel, H.; Klaczko, S. & Muller, N. (1976). *The systems theory in social sciences: Interdisciplinary systems research.* Basel: Birkhauser Verlag Publisher.

Bremer, M., Brown, J. & Canter, D. (1985). *The research interview: uses and approaches.* London: London Academic Press.

Brink, H. I. L. (1989). *Statistics for Nurses*. Pretoria: Academica.

Carte Blanche. (2000) Carte Blanche Stories: *Death by Prescription*: SABC Johannesburg; Auckland Park: Mnet

Corbie-Smith, G.; Thomas, S. B.; Williams, M.V. & Moody-Ayers, S. (1999). Attitudes and beliefs of African Americans towards participation in the medical research, *Journal of General Internal Medicine*, Vol. 14, p. 537 –546

Crossland, N. J. (1999). "Missed Opportunity*"* *GCP Journal*. Vol. 6 (2). Also online at: http://www.acrpi.com/crf/12-5 crossland.html 05/07/03

Crossland, N. J. (2000). "Compliance With GCP at the Investigator Site: Are the Lessons Learnt? *GCP Journal*. Vol. 7 (2). Also online at: http://www.acrpi.com/crf/12-5 crossland.html 05/07/03

Crossland, N. J. (2001). Achieving high standards of GCP at clinical trial units. *Clinical Research Focus*. Vol. 12 (5). Also online at: http://www.acrpi.com/crf/12-5 crossland.html 05/07/03

Dale, M. (1993). *Developing Management Skills: Techniques for improving learning and performance*. London: Kogan Page Publishers

Dal-re, R. (1992). Elements of Informed Consent in Clinical research with Drugs. A Survey of Spanish Clinical Investigators. The *Journal of Internal Medicine*, Vol. 231**,** p. 375-379.

Davies, W. K. & Longworth, N. (1997). *Lifelong learning: New vision, new implications, new roles for people, organizations, nations and communities in the 21st century*. London: Kogan Page Limited.

De Jager, J. (1990). *Active English Dictionary-for English Students*. Pretoria: Harrap Limited

Declaration of Helsinki. (2000). *Ethical Principles for Medical Research Involving Human Subjects*. Geneva.

Department of Education. (1997). *Curicullum 2005*. Pretoria

Department of Health. (2000). *Working document on good clinical practice*. Version 3. Pretoria. Also available online at:

www.south African department health.ac.za.12/23/03

Des Marchais, J. E.; Bureau, M. A.; Dumais, B. & Pigeon, G. (1992). From traditional to problem-based learning: a case report of complete curriculum reform. *Journal of Medical Education***.** 26: 190 –199.

Dewey, J. (1984). *The Foundations of Contemporary Approaches to Learning*:. In Kolb, D. A. *Experiential learning: Experience as a source of learning and development (p.*1-19). New Jersey: Prentice Hall

Duant, D. J., (2003). Clinical models: Ethnicity and recruitment rates in clinical research. *Applied Nursing Research Journal*, vol. No.3:189-195.

Dweyer, B. (2001). Successful training strategies for the twenty-first century: Using recent research on learning to provide effective training strategies. *International Journal of Educational Management*. Vol. 15 No.6: 312 – 318.

Educators in Connecticut's Pomperaug Regional School District 15. (1996). *A teachers's guide to perfomance-based learning and assessment association for supervision and curriculum development*: Virginia. Also online: http://www.med.fsu.edu/education/policies.asp.htlm 06/18/03

Edwards, A. & Talbet, R. (1999). *The hard-pressed researcher: A research handbook for the caring professions*. Second Edition. London: Longman Group Limited Publishers.

Edwards, R., Seiminski, S. & Zeldin, D. (1993). *Adult learners, education and training*. Routledge Chapman and Hall Inc.

Eitington, J. E. (1989). *The Winning Trainer*. 2nd Edition. United States of America: Gulf Publishing Company

Euro, T.; Kobayashi, T.; Inoue, K. & Yamada, Y. (1999). Development of anti-cancer drugs under new, renewed GCP from the viewpoint of drug development company developer**.** *Gan To Kagaku Ryoho*, Vol. 25 (5), p. 663-670.

Faurre, P. & Depeyrot, M. (1977)**.** *Elements of Systems Theory*. Amsterdam: North-Holland Publishing Company.

Foddy, W. (1994). *Constructing questions for interviews and questionnaires: theory and practice in social research.* United Kingdom: Cambridge University Press.

Food and Drug Administration. (2000). *Good Clinical Practice*. 85. Guidance for Industry. (Online). Available http://www.fda.gov/cvm/guidance/guide85/ 11/21/03

Food and Drug Administration. (1996). *Good Clinical Practice*. E6. Guidance for Industry. (Online). Available http://www.fda.gov/cvm/guidance/11/21/03

Food and Drug Administration. (1996). Guideline for *Good Clinical Practice*. International Conference On Harmonisation. (Online). Available at: http://www.fda.gov/ohrms/98fr/pdf/11/29/03

Food and Drug Administration. (2001). *Information for Health Professionals. Good Clinical Practice in FDA-Regulated Clinical Trials*. (Online). Available at: http://www.fda.gov/oc/gcp/default.11/29/03

Food and Drug Administration. (2001). *Regulations Relating to Good Clinical Practice in FDA-Regulated Clinical Trials*. (Online). Available at: http://www.fda.gov/oc/gcp/regulations.html11/30/03

Food and Drug Administration. (2002). *Institution Review Board(IRB/Ethics Committees) Information Sheets-Websites of Interest on Good Clinical Practice in FDA-Regulated Clinical Trials*. (Online). Available at: http://www.fda.gov/oc/ohrt/irbs/websites.html/11/29/03

Franzen, M. D. (1989). *Reliability and validity in neuropsychological assessment. critical issues in neoropsychology*. London: Plenum Press.

Freedman, L. S.; Simon, R.; Foulkes, M. A. et.al. (1995). Inclusion of women and minorities in clinical trials and the NIH revitalization act of 1993: The perspective of NIH clinical trialists. *Controlled Clinical Trials*, Vol. 16: 277 - 309

Furman, S.H. & Malen, B., (1991). *The politics of curriculum and testing*. Bristol: The Falmer Press

Gibbs, G. (1988). *Learning by doing. A guide to teaching and learning methods*. United Kingdom: Further Education Unit

Gillies, D. A. (1994). *Nursing management: a systems approach*. London: W. B. Saunders Company.

Gotlieb, S. (2000). Breast Cancer Researcher Accused of Serious Scientific Misconduct. *British Medical Journal*. V320: p.398 – 399

Grant, J. S & Davis, L. L. (1997). Selection and use of content experts for instrument development, *Res. Nurs. Health*, 20 (3), 269-274

Gual, A. (1998). *The International conference of harmonization of GCP guidelines*. United States of America: Durhaw.

Harris, Y.; Gorelick, P.B.; Samuels, P. & Bempong, I. (1996). Why African Americans May Not be Participating in Clinical Trials, *Journal of National Medical Association*, Vol. 88, p.630 -634

Havelock, R. G. (1971). *The change agent's guide to innovation in education*. Engelwood Cliff: N. J. Educational Technology Publications.

Havelock, R.G. & Huberman, A. M. (1977). *Solving educational problems: The theory and reality of innovation in developing countries.* UNESCO. Switzerland: Journal de Geneva Publishers.

Havelock,R. G. (1982). *The change agents guide to innovation in education*. New Jersey: Educational Technology Publications.

Heilman, R. (1995). Drug Development History: " Overview" and What are GCPs? *Quality Assurance Journal*. Volume 4 (1) p. 75 – 79.

Holaday, M. & Smith, A. (1995). Coping skills training: Evaluating a training model. *A Journal of Mental Health Counseling*. Vol. 17. (3). p. 360-369.

Jarvis, P. (1996). *Adult and continuing education*: *Theory and practice*. 2nd Edition. : London: British Library of Publication Data.

Johnson, D. E. (1974). Development of Theory: A requisite for nursing as a primary health profession. *Nursing Research*, 23 (5): 372 – 377.

Johnson, S. K., Geroy, G. D., & Griego, O. V. (1999). Career development international. the mentoring model theory*: Dimentions in mentoring protocols*. Vol. 4 (7): 384 – 391.

Jones, M. & Mann, P. (1992). *HRD: International perspectives on developing and learning.* United States of America: McNaughton & Gunn, Inc.

Kirkwood, B. R. (1988). *The Essentials of Medical Statistics*. Oxford: Blackwell Scientific Publications.

Klir, G. (1972). *Study of Organisations of Self Organising Systems in Proc. 6th International Congress on Cybernetics*. Walmer Publishers: Belgium

Knowles, M. S., (1980). *The modern practice of adult models of teaching*. Philadelphia: F. A. Davis.

Kolb, D. A. (1984). *Experiential learning. experience as a source of learning and development.* New Jersey: Prentice-Hall

Komen, S. G. (1999). Women unaware of clinical trials. *New England Journal*. Vol. 341(1): p. 2061 – 2067

Kreber, C. (1998). The relationships between self-directed learning, critical thinking, psychological type and some implications for teaching in higher education. *Studies in Higher Education*. Vol. 23(1): 71 – 86

Kusche, J. (1993). *Good clinical practice and physiotherapy. Methods found in experimental clinical pharmacology*, Vol. 15 (4): 241-247

Lauffer, A. (1982). *Assessment tools for practitioners, managers and trainers: Sage Human Services Guides.* Bervely Hills: Sage Publications

Leedy, P. (1993). *Practical research. planning and design*. New York: Mac Millan Publishing Company.

Lo, B., Wolf, L.E. & Berkeley, A. (2000). Conflict if interest policies for investigators in clinical trials. *New English Journal of Medicine*, Vol. 343 (3): 1616-1620.

Madaus, G. F.; Scriven, M. S & Stuffelbeam, D. L. (1987). *Evaluation models: Viewpoints on educational and human services evaluation. United States of America:* Kluwer Academic Publishers.

Madaus, G. F.; Stuffelbeam, D. L. & Tyler, R. W.; (1989). *Educational evaluation: Classic works of Ralph W. Tyler*. Boston: Kluwer Academic Publishers.

Mandison, G. (1982). *Understanding: A phenomenological pragmatic analysis.* London: Greenwood Press.

Manyike, P.(2003). *Inequitable access to clinical trial services: The less explored last health care frontier*. Unpublished Work

Marton, F, (1975) *Beyond the information given, in Entwistle N and Hounsell D (eds) How students learn.* Lancaster: University of Lancaster.

Mastaglia, B., Toye, C. & Christjanson, L. J. (2003). Ensuring content validity in instrument development: Challenges and innovative approaches, *Contemp Nurse*, 14 (3): 281- 291

Mateo, M. A., & Kirchoff, K. T., (1999). 2nd Edition. *Using and conducting nursing research in the clinical setting***.** W. B. Saunders Publishers: Philadelphia.

Mcalpine, H.; Kristjanson, L. & Poroch, D. (1997) Development and testing of the ethical reasoning tool (ERT): An instrument to measure the ethical reasoning for nurses, *Journal of Advanced Nursing*, 25 (6): 1151 – 1161.

McDowell, I. & Newell, C. (1987)**.** *Measuring health: A guide to rating scales and questionnaires*. Oxford: Oxford University Press.

McIntyre, J. & Byrd, D. (2000). *Research on effective models for teacher education.* United States Of America: Corwin Press Inc.

McNiff, J.; Lomax, P. & Whitehead, J. (2000). *You and your action research project.* New York: Hyde Publications.

Medical Research Council (MRC). (1998). *Guidelines For Good Clinical Practice in Clinical Trials. Mitcham, Surey*: MRC Publication Department.

Medicines and Related Substances Control Act 101 0f 1965 as Amended. (1965). Pretoria: Department of Health.

Meleis, A. I. (1985). *Theoretical nursing: Development and progress.* Philadelphia: J.B. Lippincot Company.

Montgomery, D. C. (1976). *Design and Analysis of Experience*. New York: John Wiley Publishers.

Moore, M. L. (1997). Recruitment and retention: Nursing research among low-income pregnant women. *Applied Nursing Research*, 10 (2): 152 – 158.

Morse, E. V.; Simon, P. M.; Bosch, C. L. & Walker, J. (1995). Issues of recruitment, retention and compliance in community- based clinical trials with traditionally underserved populations. *Applied Nursing Research*, 8 (1) 8-14

Murk, P. F.; Barrett, A. J. & Atchade, P. F. (2000). Diagnostic techniques for training and education: Strategies for marketing and economic development. *Journal of Workplace Learning*. Vol. 12.(7) :296-306.

Newman, L. A. Pollock, R. E. & Johnson-Thompson, M. C. (2003). Increasing the pool of academically oriented African-American medical and surgical oncologists, *Cancer Journal*, 97 (1) 329 - 334

Nijhof, W. J. & Streumer, J. N. 1998. *New Roles and Training Models for Managers in the Printing and Communications Industry in Netherlands.* Oxford: Blackwell Publishers Ltd.

Norman, G. R. (1988). Problem solving skills, solving problems and problem based learning. *Medical Education Journal*, 22 (9): 279 – 286

Olin, J. T.; Dagerman, K. S.; Fox, L. S.; Bower,B. & Schneider, L. S. 2002. Increasing Ethnic Minority Participation in Alzheimers Disease Research. *Alzheimer Dis Assoc Disord*. 2 : 82 – 85

Payne, S. L. 1973. *The Art of Asking Questions*. New Jersey: Princeton University Press.

Pharmaceutical Medical Association (PMA). 2000. *List of Pharmaceutical Industries in South Africa.* Johannesburg: PMA

Pletsch, P. K. ; Llowe, C. & Teny, M. 1995. Recruitment of Minority Subjects for Intervention Research. Image: *Journal of Nursing Scholarship*, 27 (3), 211 – 215.

Polit, J, & Hungler, B. 1991. *Nursing Research: Principles and Methods*. 3rd Edition. Philadelphia: J.B. Lippincot Company.

Printich, P. R. & DeGroot, E. V. 1990. Motivational and Self Regulated Learning Components of Classroom Academic Performance. *Journal of Educational Psychology*. Vol. 82: 33-40.

Pruitt, R. H. & Privette, A. B. 2001. Planning Strategies for the Avoidance of Pitfalls in Intervention Research. *Journal of Advanced Nursing*. 35 (4): 514 – 520

Putt, A. M. 1989. *General Systems Theory Applied to Nursing.* Cambridge: Harvard University Press

Raven, A. 1993. *Clinical Trials: An Introduction*. 2nd Edition. Oxford, New York: Redlciffe Medical Press.

Reviere, R., Berkowitz, S., Carter, C. C. & Ferguson, C. G. 1996. *Needs Assessment: A Creative and Practical Guide for Social Scientists.* United States of America: Taylor & Francis Publishers.

Reynolds, P. D. 1982. *Ethics and Social Science Research*. London: Prentice-Hall International Inc.

Roberts-DeGennaro, M. 1996. An Interdisciplinary Training Model in the Field of Early Intervention. *Social work in Education.* Vol. 18 (1): 99-119.

Sharts-Hopko, N. 1999. The Challenge of Minority Recruitment into Research Protocols**.** *DNA Reporter,* 24 (1), 18 –19.

Sidley, P. 2001. Audit Team Finds Further Faults with Doctor's Results. *British Medical Journal*. 322: 1143 - 344

Sinclair, J. 1995. *Collins Cobuild English Usage*. Herper Collins Publishers: Glasgow.

Small, R.; Yelland, J.; Lumley, J. & Rice, P.L. 1999. Cross-cultural Research: Trying to Do it Better: Issues of Study Design, *Aust N Z J Public Health*, Vol. 23:385 – 389

Sproull, N. 1988. *Handbook of Research Methods: a Guide for Practitioners and Students in the Social Sciences*. London: The Scarecrow Press, Inc.

St. Vrain Valley School District. 2003. *Training Materials Model Professional Development Credit*. London: Tyra Information Strategies Inc.

Stark, N; Puskell, R.; Bell, R.; Cooper, M. R.; Walker, b. Wilson, A.; & Talum, C. 2002. Increasing Participation in Cancer Clinical Trials: Summary of the " Moving Beyond the Barriers" Conference in North Carolina. *Journal of The National Medical Association,* 94 (1):

31-39.

Stata Corporation. 2001. *Stata Statistical Software*. Release 7.0. College Station; TX: Stata Corporation.

Stone, P.W. & Tourangeau, A.E. 2003. Measuring Nursing Services in Patient Safety Research. *Applied Nursing Research***.** Vol. 6 (2): 39 - 43

Stuffelbeam, D. L., Foley, W. J., Gephart, W. J., Guba, E. G., Hammond, R. L., Merrimantt, P., and Provus, M. W. 1971. *Educational Evaluation and Decision-Making*. Itasca Inc.: Peacorts

Stykes, J. B. 1982. *The Pocket Oxford Dictionary of Current English.* Britain: University Press.

Swanson, G. M. & Ward, A. J. 1995. Recruiting Minorities Into Clinical Trials. Towards a Participant-Friendly System. *Journal of the National Cancer Institute*, 87 (23), 1747 –1759.

Tan, C. M. 1992. An Evaluation of the Use of Continuous Assessment in the Teaching of Physiology. *Higher Education* 23: 255 – 272

Thomas, S. B. & Quinn, S. C. 1991. The Tuskegee Syphilis Study, 1932 to 1972: Implications for HIV Education and AIDS Risk Education Programs in the Black Community. *American Journal of Public Health.* Vol.8 (1): 1498 - 1505

Truelove, S. 1995. *Handbook of Training and Development***.** **(**2nd Edition). Blackwell Publishers: Oxford

Vogt, W. P., 1993. *Dictionary of Statistics and Methodology: A non Technical Guide***.** Newbury Park. CA: Sage

Von Bertalanffy, L. 1973. *General Systems Theory: Foundations, Development Application.* New York: George Braziller Inc.

Wainwright, D. 1997. Can Sociological Research Be Qualitative, Critical and Valid? *The Qualitative Report.* Vol. 3 (2) (http://www.nova.edu/sss/QR/QR3-2/wain.html-8/3/2003)

Walters, S. (1997) *Globalisation, Adult Education and Training: Impacts and Issues.* Cape Town: CACE Publications

Waters, C. M. 1996. Professional Development in Nursing Research: a Culturally Diverse Postdoctoral Experience, *Image J Nurs. Sch.*, 28 (1): 47 – 50

Welsh, J.L.; Adam, P.; Fontaine, P. & Gjerdingen, D. 2002. Recruiting for a Randomised Controlled Trial From an Ethnically Diverse Population: Lessons From Martenal Infection and Preterm Labour Study. *The Journal of Family Practice*, V51 (9): 760 – 766

WHO, 1994. *Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products. Responsibilities of Investigator*. Geneva: Switzerland.

. Wicklund, R.A. & Brehim, J.W. 1976. *Perspectives on Cognitive Dissonance.* New York: Lawrence Erlbaum Associate Publishers.

Witkins, B. R. 1984. *Assessing Needs in Educational and Social Programs*. (1st Edition). Carlifornia: Jessey-Bass Inc. Publishers.

Wu, A. W.; Folkman, S.; McPhee, S. J. & Lo, B. 2003. Do house Officers Learn From their Mistakes? *Qual Saf Health Care* 12 (3): 221-226

Zhang X.; Wang, L.; Zhu, X.; Wang, K. 1999, Knowledge, Attitude and Practice Survey on Immunization Service Delivery in Ghangxi and Gansi of China. *Social Sciences and Medicine***,** V49 (1: 8): 1125 – 1127

**Annexure 1**

20 Jersey Road
Dinwiddie
GERMISTON
1401
04 June 2003

THE RESPONDENT:
STATEMENT OF CONSENT

This letter serves to request your participation in a research project that will include the questionnaire attached. The information gathered out of this questionnaire will help in identification of possible training needs with regards to GCP and conduct of clinical trials. The results will assist in the development of a GCP training model for both clinical investigators and study co-ordinators so as to inform "Gold" standard in the conduct of clinical trials in South Africa.

The writer is a PhD student at the University of Western Cape and doing research as part of the course requirements. You are requested to complete a questionnaire, taking + / - 10 minutes of your off-duty / free time. This is not a difficult questionnaire, your current knowledge base and experience in the conduct of clinical trials will be sufficient. You were randomly selected because you are part of clinical trial investigators / study co-ordinators involved in the conduct of clinical trials in South Africa.

Participation is **voluntarily** done. You have a right to refuse to participate, or answer any specific question. You can also withdraw at any point after starting to answer the questionnaire. If you decide not to participate or withdraw, just return the blank or incomplete questionnaire using the self addressed envelope provided. You do not have to mention your name. The number on the right hand side of your questionnaire is for identification by the researcher. You may also reply by fax if unable to complete the questionnaire during my presence. Completion of the questionnaire, will be regarded as giving consent.

Your participation in this research is **confidential**. No reports of this study will identify the respondent at any point. Your refusal to participate will not affect your future involvement / selection in conducting clinical trials.

You will **benefit** from participating in this project that is of value to the medical sciences, clinical research and the community at large, as the results may contribute in identification of training needs and in developing a GCP training model for clinical investigators and study co-ordinator to ensure their competency when they get involved in conducting clinical trials.

The **results** will be given to you, should you ask for them. In case of any questions about the project or your rights as a participant, you can contact me at the above address or at 082 457 4841.

Yours faithfully,

**NOMUSA RAPHESU**

**ANNEXURE 2:**

# UNIVERSITY OF THE WESTERN CAPE

**FACULTY OF COMMUNITY HEALTH SCIENCES**

HIGHER DEGREES COMMITTEE

## (GGHD2002/09)

**REPORT TO FACULTY BOARD OF A MEETING OF THE ABOVE COMMITTEE WHICH WAS HELD ON FRIDAY, 29 NOVEMBER 2002 AT 10H00 IN THE CONFERENCE ROOM, COMMUNITY AND HEALTH SCIENCES FACULTY.**

**RESEARCH PROPOSAL**

| | |
|---|---|
| **Candidate:** | **N J Raphesu (2109707) GGHD Annex 2002/09/08** |
| **Course:** | D. Cur |
| **Department:** | Nursing |
| **Research Title:** | **The Development of a good clinical practice training model for use in South African Clinical trials** |
| **Supervisor:** | **Prof E Kortenbout** |
| **10 keywords** | Good Clinical practice (GCP), training model, clinical investigator, study co-ordinator, adverse event, trial subject, clinical trial, investigational drug, Standard Operational Procedure (SOP), Training needs instrument |

**Accepted and recommended to senate.**

## ANNEXURE 3:

**ASSESSMENT OF GCP TRAINING NEEDS** No: 001

***SECTION 1:***

Please √ in the appropriate box, or fill in the requested information as per question requirement.

| | | |
|---|---|---|
| 1. | **GENDER** | |
| | | |
| | Male | ☐ |
| | Female | ☐ |
| | | |
| 2. | **NAME YOUR HIGHEST QUALIFICATION (Tick the appropriate space)** | |
| | | |
| | MBChB | ☐ |
| | M.Med / Masters degree | ☐ |
| | Bacheor's Degree | ☐ |
| | Honours | ☐ |
| | Other (specify) | ☐ |
| | | |
| 3. | **WHERE HAVE YOU CONDUCTED TRIALS IN THE PAST? ( Please tick all relevant)** | |
| | | |
| | Private Sector | ☐ |
| | Academic / University | ☐ |
| | Other (specify) | ☐ |
| | | |
| 4. | ARE YOU CURRENTLY INVOLVED IN CONDUCTING CLINICAL TRIALS? | |
| | YES | ☐ |
| | NO | ☐ |
| 5. | **WHAT IS YOUR CURRENT ROLE? (Tick the applicable role)** | |
| | Please indicate how long, have you been working in this capacity ? | |
| | Principal Investigator | ☐ |
| | Study co-ordinator | ☐ |
| | Co/sub-investigator | ☐ |
| | Other (please specify) | ☐ |
| | | ☐ |
| | | |

**SECTION 2:**

| | | |
|---|---|---|
| 1. | **Have you been trained in GCP?** | |
| | Yes | ☐ |
| | No | ☐ |
| | | |
| 2. | **How did you obtain training / knowledge? (Tick all applicable)** | |
| | Formal training by training organizations | ☐ |
| | Informal training – during start-up meeting | ☐ |
| | Reading material on GCP | ☐ |
| | Other (specify) | ☐ |
| | | |
| 3. | **Do you feel you need more training on GCP?** | |
| | Yes: | ☐ |
| | No: | ☐ |
| | Please give reasons for your response. | |
| | | |
| 4. | **If yes, in which area? (Tick all applicable)** | |
| | Informed consent | ☐ |
| | SDV | ☐ |
| | Investigator responsibility | ☐ |
| | Agreements | ☐ |
| | Patient Safety | ☐ |
| | Quality assurance | ☐ |
| | Data Handling | ☐ |
| | Other (please specify) | ☐ |
| | | |
| 5. | **Do you have suggestion of additional information to be included in the GCP Training Program?** | |
| | Yes | ☐ |
| | No | ☐ |
| | If yes, please give your suggestions below in the area provided:- | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

***SECTION 3:***

**ANSWER THE FOLLOWING QUESTIONS**

| | | |
|---|---|---|
| 1. | **How much time per day do you allocate to spend with monitors at your site? (tick what is applicable)** | |
| | None | ☐ |
| | 1-2 hours | ☐ |
| | 3-4 hours | ☐ |
| | Half day | ☐ |
| | Other (specify) | ☐ |
| | | |
| 2 | **What do you do in the following situations involving clinical trial patients?** | |
| | - a patient presents with an unusual symptom. | |
| | - a patient misses a scheduled visit | |
| | - a patient wants to withdraw from the study | |
| | - a patient is unsure of how to complete a questionnaire | |
| | | |
| 3 | **State two aims of GCP** | |
| | 1. | |
| | 2. | |
| | | |
| 4 | Name **any 2 kinds of agreements that investigator signs before/during site initiation?** **1.** | |
| | 2. | |
| | | |
| 5. | **Do you have suggestions of additional information to be included in the Planned GCP Training Program?** | |
| | Yes | ☐ |
| | No | ☐ |
| | If yes, describe or list the most important areas to be covered | |
| | | |
| | | |
| | | |
| | | |
| | | |

| | | |
|---|---|---|
| | ***INFORMED CONSENT FORM*** | |
| 6. | Will you include:<br>**(a)**- an inviting statement for the patient to participate in the study? | |
| | YES | ☐ |
| | NO | ☐ |
| | UNSURE | ☐ |
| | **(b**) – do you ensure that patient's involvement in the study is preceded by:<br>(Tick what is applicable) | |
| | - Verbal explanation | ☐ |
| | - Written information leaflet and signed informed consent | ☐ |
| | - Signed document | ☐ |
| | - Study related procedure / investigation | ☐ |
| | **(c**) Will you tell the patient about the:-<br>- **risks** of participating to the study? (Please substantiate your answer) | |
| | - | |
| | - | |
| | - **benefits** of participating into the study | |
| | - | |
| | - | |
| | **(d)** Why should the patient be given a copy of signed informed consent? | |
| | | |
| | | |

***SECTION 4:***

| | | |
|---|---|---|
| 1. | **Are you well versed with the 2000 Declaration of Helsinki?** | |
| | Yes | ☐ |
| | No | ☐ |
| | If yes, do you have any comments: | |
| 2. | **What is the time frame for reporting on SAE?** | |
| | | |
| 3. | **Do the sponsors always supply you with a copy of GCP?** | |
| | Yes | ☐ |
| | No | ☐ |
| 4 | What do you do in the following scenarios?<br>**( a )** find that the wrong date is entered in Case Report File (CRF) page | |
| | ( b) a known AE becomes serious | |

| | | |
|---|---|---|
| 5. | Apart from sponsor, who should be notified of an SAE? | |
| | | |
| 6 | Have you ever done Ethics application? | |
| | 1.YES | ☐ |
| | 2. NO | ☐ |
| | | |
| 7. | **Will / do you explain to the patient the procedures involved in the study?** | |
| | Yes | ☐ |
| | No | ☐ |
| 8 | Will you tell the patient about risks/benefits involved in participating in the particular study?<br>**Please substantiate your answer.** | |
| | | |
| 9 | Why should you have 2 copies of informed consents? | |
| | | |
| | | |
| 10 | **In your opinion, who should do the Ethics Committee application?** | |
| | Sponsor | ☐ |
| | Investigator | ☐ |
| | Unsure | ☐ |

**SECTION 5:**

| | | |
|---|---|---|
| 1. | What is your comment about the following? | |
| | - Financial Interest Disclosure to MCC & Ethics | |
| | - Placebo-controlled trials | |
| | - Supply of medication to patients post trial | |
| | - The regulatory body (MCC) interest in the number of studies each site is conducting | |
| 2. | Is GCP training given during start-up meetings (**tick the appropriate)** | |
| | Adequate | ☐ |
| | Inadequate | ☐ |
| | Unsure | ☐ |
| | | |
| 3. | Name any 3 factors that affect your GCP implementation in your work place:- | |
| | 1. | |
| | 2. | |
| | 3. | |
| | | |

**SECTION 6:**

| | | |
|---|---|---|
| 1. | **How much time at an average do you spend getting an informed consent?** | |
| 2. | **What are the common reasons that that contribute to the withdrawal of patients from the study?** | |
| 3. | **Have you ever heard of Data protection Act / Directive? Please explain** | |
| | | |
| 4. | **What do you tell your patients about the risks of participating in the study?** | |
| | | |
| | | |
| 5. | **Have you read (2000) Dept. of Health GCP Guidelines?** | |
| | **YES** | ☐ |
| | **NO** | ☐ |

| | | |
|---|---|---|
| | | |
| 6. | **If yes, please identify key provisions:** | |
| | **(a)** | |
| | **(b)** | |
| | **(c )** | |
| | **(d)** | |
| | **(e)** | |
| 7. | **Do you have any problem in applying these Guidelines?** | |
| | **YES** | ☐ |
| | **NO** | ☐ |
| | **(Please specify)** | |
| 8. | **Have you attended any GCP course before?** | |
| | **1.YES** | ☐ |
| | **2. NO** | ☐ |
| | **If no, would you like to attend one?** | |
| | | |
| 9. | **What are the topics that you would like to see covered on a GCP course?** | |
| | | |
| 10 | What do you recommend for the sponsor to do, in improving your conduct of clinical trials? | |
| | | |

**THANK YOU FOR YOUR TIME AND ASSISTANCE**

## ANNEXURE 4:

**ASSESSMENT OF GCP TRAINING NEEDS No: 001**

**SECTION 1:**

**Please √ in the appropriate box, or fill in the requested information as per question requirement.**

| | | |
|---|---|---|
| **1.** | **GENDER** | |
| | | |
| | **Male** | |
| | **Female** | |
| | | |
| **2.** | **NAME YOUR HIGHEST QUALIFICATION (Tick the appropriate space)** | |
| | | |
| | **MBChB** | |
| | **M.Med / Masters degree** | |
| | **Bacheor's Degree** | |
| | **Honours** | |
| | **Other (specify)** | |
| | | |
| **3.** | **WHERE HAVE YOU CONDUCTED TRIALS IN THE PAST? ( Please tick all relevant)** | |
| | | |
| | **Private Sector** | |
| | **Academic / University** | |
| | **Other (specify)** | |

| | | |
|---|---|---|
| | | |
| 4. | **ARE YOU CURRENTLY INVOLVED IN CONDUCTING CLINICAL TRIALS?** | |
| | **YES** | |
| | **NO** | |
| 5. | **WHAT IS YOUR CURRENT ROLE? (Tick the applicable role)** | |
| | | |
| | **Principal Investigator** | |
| | **Study co-ordinator** | |
| | **Co/sub-investigator** | |
| | **Other (please specify)** | |
| | **Please indicate how long, have you been working in this capacity ?** | |
| | | |

| | | |
|---|---|---|
| **1** | *Have you been trained in GCP* | |
| | *Yes* | |
| | *No* | |
| **2.** | ***How did you obtain training / knowledge? (Tick all applicable)*** | |
| | **Formal training by training organizations** | |
| | **Informal training – during start-up meeting** | |
| | **Reading material on GCP** | |
| | **Other (specify)** | |
| | | |
| **3.** | **Do you feel you need more training on GCP?** | |
| | **Yes:** | |
| | **No:** | |
| | **Please give reasons for your response.** | |
| | | |
| **4.** | **If yes, in which area? (Tick all applicable)** | |
| | **Informed consent** | |
| | **Source Data Verification (SDV)** | |
| | **Investigator responsibility** | |
| | **Agreements** | |
| | **Patient Safety** | |
| | **Quality assurance** | |
| | **Data Handling** | |
| | **Other (please specify)** | |
| | | |
| **5.** | *Do you have suggestion of additional information to be included in the GCP Training Program*? | |
| | **Yes** | |
| | **No** | |

**SECTION 3: ANSWER THE FOLLOWING QUESTIONS**

| | | |
|---|---|---|
| **1.** | **How much time per day do you allocate to spend with monitors at your site? (tick what is applicable)** | |
| | **None** | |
| | **1-2 hours** | |
| | **3-4 hours** | |
| | **Half day** | |
| | **Other (specify)** | |
| | | |
| **2** | **What do you do in the following situations involving clinical trial patients?** | |
| | **a patient presents with an unusual symptom.** | |
| | **a patient misses a scheduled visit** | |
| | **a patient wants to withdraw from the study** | |
| | **a patient is unsure of how to complete a questionnaire** | |
| | | |
| **3** | **State two aims of GCP** | |
| | **1.** | |
| | **2.** | |

| | | |
|---|---|---|
| | | |
| 4 | **Name any 2 kinds of agreements that investigator signs before/during site initiation?**<br>**1.** | |
| | **2.** | |
| | | |
| **5.** | **Do you have suggestions of additional information to be included in the**<br>**Planned GCP Training Program?** | |
| | **Yes** | |
| | **No** | |
| | **If yes, describe or list the most important areas to be covered** | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | ***INFORMED CONSENT FORM*** | |
| **6.** | **Will you include:**<br>**(a)- an inviting statement for the patient to participate in the study?** | |

| | | |
|---|---|---|
| | **YES** | |
| | **NO** | |
| | **UNSURE** | |
| | **(b) – do you ensure that patient's involvement in the study is preceded by:**<br>**(Tick what is applicable)** | |
| | **Verbal explanation** | |
| | **Written information leaflet and signed informed consent** | |
| | **Signed document** | |
| | **Study related procedure / investigation** | |
| | **(c) Will you tell the patient about the:-**<br>**risks of participating to the study? (Please substantiate your answer)** | |
| | | |
| | | |
| | **benefits of participating into the study** | |
| | | |
| | | |
| | **(d) Why should the patient be given a copy of signed informed consent?** | |
| | | |

**SECTION 4:**

| | | |
|---|---|---|
| **1.** | **Are you well versed with the 2000 Declaration of Helsinki?** | |
| | **Yes** | ☐ |
| | **No** | ☐ |
| | **If yes, do you have any comments:** | |
| **2.** | **What is the time frame for reporting on SAE?** | |
| | | |
| **3.** | **Do the sponsors always supply you with a copy of GCP?** | |
| | **Yes** | ☐ |
| | **No** | ☐ |
| **4** | **What do you do in the following scenarios?( a ) find that the wrong date is entered in Case Report File (CRF) page** | |
| | **( b) a known AE becomes serious** | |
| **5.** | **Apart from sponsor, who should be notified of an SAE?** | |
| | | |

| | | |
|---|---|---|
| **6** | **Have you ever done Ethics application?** | |
| | **1.YES** | |
| | **2. NO** | |
| | | |
| **7.** | **Will / do you explain to the patient the procedures involved in the study?** | |
| | **Yes** | |
| | **No** | |
| **8** | **Will you tell the patient about risks/benefits involved in participating in the particular study?**<br><br>**Please substantiate your answer.** | |
| |  | |
| **9** | **Why should you have 2 copies of informed consents?** | |
| | | |
| | | |
| **10** | **In your opinion, who should do the Ethics Committee application?** | |
| | **Sponsor** | |
| | **Investigator** | |
| | **Unsure** | |

**SECTION 5:**

| | | |
|---|---|---|
| **1.** | **What is your comment about the following?** | |
| | **Financial Interest Disclosure to MCC & Ethics** | |
| | **Placebo-controlled trials** | |
| | **Supply of medication to patients post trial** | |
| | **The regulatory body (MCC) interest in the number of studies each site is conducting** | |
| **2.** | **Is GCP training given during start-up meetings (tick the appropriate)** | |
| | **Adequate** | |
| | **Inadequate** | |
| | **Unsure** | |
| | | |
| **3.** | **Name any 3 factors that affect your GCP implementation in your work place:-** | |
| | **1.** | |
| | **2.** | |
| | **3.** | |

**SECTION 6:**

| | | |
|---|---|---|
| **1** | **How much time at an average do you spend getting an informed consent?** | |
| | | |
| **2** | **What are the common reasons that that contribute to the withdrawal of patients from the study?** | |
| | | |
| **3** | **Have you ever heard of Data protection Act / Directive? Please explain** | |
| | | |
| | | |
| **4** | **What do you tell your patients about the risks of participating in the study?** | |
| | | |
| | | |
| **5** | **Have you read (2000) Dept. of Health GCP Guidelines?** | |
| | **YES** | |
| | **NO** | |
| | | |

| | | |
|---|---|---|
| **6** | **If yes, please identify key provisions:** | |
| | **(a)** | |
| | **(b)** | |
| | **(c )** | |
| | **(d)** | |
| | **(e)** | |
| **7** | **Do you have any problem in applying these Guidelines?** | |
| | **YES** | |
| | **NO** | |
| | **(Please specify)** | |
| **8** | **Have you attended any GCP course before?** | |
| | **1.YES** | |
| | **2. NO** | |
| | **If no, would you like to attend one?** | |
| | | |
| **9** | **What are the topics that you would like to see covered on a GCP course?** | |
| | | |
| | | |
| | | |
| | | |

| | | |
|---|---|---|
| **10** | **What do you recommend for the sponsor to do, in improving your conduct of clinical trials?** | |
| | | |
| | | |
| | | |

THANK YOU FOR YOUR TIME AND ASSISTANCE

**ANNEXURE 5:**

# ASSESSMENT OF GCP TRAINING NEEDS

No: 001

## *SECTION 1:*

Please √ in the appropriate box, or fill in the requested information as per question requirement.

| | | |
|---|---|---|
| 1. | **GENDER** | |
| | | |
| | Male | 1 |
| | Female | 2 |
| | | |
| 2. | **NAME YOUR HIGHEST QUALIFICATION (Tick the appropriate space)** | |
| | | |
| | MBChB | 1 |
| | M.Med / Masters degree | 2 |
| | Bacheor's Degree | 3 |
| | Honours | 4 |
| | Other (specify) | specify |
| | | |
| 3. | **WHERE HAVE YOU CONDUCTED TRIALS IN THE PAST? ( Please tick all relevant)** | |
| | | |
| | Private Sector | 1 |
| | Academic / University | 2 |
| | Other (specify) | 3 |
| | | |
| 4. | ARE YOU CURRENTLY INVOLVED IN CONDUCTING CLINICAL TRIALS? | |
| | YES | **1** |
| | NO | **2** |
| 5. | **WHAT IS YOUR CURRENT ROLE? (Tick the applicable role)** | |
| | | |
| | Principal Investigator | **1** |
| | Study co-ordinator | **2** |
| | Co/sub-investigator | 3 |
| | Other (please specify) | Specify |
| | Please indicate how long, have you been working in this capacity / | Months/yrs |
| | | |

SECTION 2:

| | | |
|---|---|---|
| 1. | **Have you been trained in GCP?** | |
| | Yes | 1 |
| | No | 2 |
| | | |
| 2. | **How did you obtain training / knowledge? (Tick all applicable)** | |
| | Formal training by training organizations | 1 |
| | Informal training – during start-up meeting | 2 |
| | Reading material on GCP | 3 |
| | Other (specify) | specify |
| | | |
| 3. | **Do you feel you need more training on GCP?** | |
| | Yes: | 1 |
| | No: | 2 |
| | Please give reasons for your response. | Specify |
| | | |
| 4. | **If yes, in which area? (Tick all applicable)** | |
| | Informed consent | 1 |
| | Source Data Verification (SDV) | 2 |
| | Investigator responsibility | 3 |
| | Agreements | 4 |
| | Patient Safety | 5 |
| | Quality assurance | 6 |
| | Data Handling | 7 |
| | Other (please specify) | Specify |
| | | |
| 5. | **Do you have suggestion of additional information to be included in the GCP Training Program?** | |
| | Yes | 1 |
| | No | 2 |
| | If yes, please give your suggestions below in the area provided:- | Specify |
| | | |

**SECTION 3:**

**ANSWER THE FOLLOWING QUESTIONS**

| | | |
|---|---|---|
| 1. | **How much time per day do you allocate to spend with monitors at your site? (tick what is applicable)** | |
| | None | 1 |
| | 1-2 hours | 2 |
| | 3-4 hours | 3 |
| | Half day | 4 |
| | Other (specify) | Specify |
| | | |
| 2 | **What do you do in the following situations involving clinical trial patients?** | |
| | - a patient presents with an unusual symptom.<br>*Treat as an AE, record in CRF, report depending on your position & type of trial* | Correct answer =1<br>Wrong =0 |
| | - a patient misses a scheduled visit<br><br>do follow-up, reschedule if within window period, contact sponsor for waiver if needed, all depends on type of trial & your position. a file note may be needed. | |
| | - a patient wants to withdraw from the study<br>Get a reason, counsel, do not force continuation, withdraw if patient insists, and arrange alternative treatment. Do termination visit if required. Document in CRF. | |
| | - a patient is unsure of how to complete a questionnaire<br>re-educate, re-counsel, explain but do not complete for him,/her nor influence | |
| | | |
| 3 | **State two aims of GCP** | |
| | 1. = Quality Data | 1 |
| | 2. = Patient's safety | 1 |
| | | |
| 4 | Name **any 2 kinds of agreements that investigator signs before/during site initiation?**<br>**1. =** confidentiality = 1 | |
| | 2. = financial = 1<br>Other agreements = protocol / study; SCA (standard clarification | |

| | | |
|---|---|---|
| | agreement) | |
| | | |
| 5. | **Do you have suggestions of additional information to be included in the planned GCP Training Program?** | |
| | Yes | 1 |
| | No | 2 |
| | If yes, describe or list the most important areas to be covered | specify |
| | | |
| | | |
| | | |
| | | |
| | | |
| | **INFORMED CONSENT FORM** | |
| 6. | Will you include:<br>**(a)**- an inviting statement for the patient to participate in the study? | |
| | YES | 1 |
| | NO | 2 |
| | UNSURE | 3 |
| | **(b**) – do you ensure that patient's involvement in the study is preceded by: (Tick what is applicable) | |
| | - Verbal explanation | 1 |
| | - Written information leaflet and signed informed consent | 1 |
| | - Signed document | 1 |
| | - Study related procedure / investigation | 1 |
| | **(c**) Will you tell the patient about the:-<br>- **risks** of participating to the study? (Please substantiate your answer) | Yes = 1<br>No = 2 |
| | - Specify | |
| | - Specify | |
| | - **benefits** of participating into the study | |
| | - specify | |
| | - specify | |
| | **(d)** Why should the patient be given a copy of signed informed consent? | |
| | A legal document & pt has a right to have a copy | |
| | For referral purposes re trial & contacts, future use in case of needs or problems | |

***SECTION 4:***

| | | |
|---|---|---|
| 1. | **Are you well versed with the 2000 Declaration of Helsinki?** | |
| | Yes | 1 |
| | No | 2 |
| | If yes, do you have any comments: | Specify |
| 2. | **What is the time frame for reporting on SAE?** | 24hrs=1 |
| | | Wrong = 0 |
| 3. | **Do the sponsors always supply you with a copy of GCP?** | |
| | Yes | 1 |
| | No | 2 |
| 4 | What do you do in the following scenarios?<br>**( a )** find that the wrong date is entered in Case Report File (CRF) page<br>cancel by drawing a straight line across, enter the correct date, sign and initial | Correct = 1<br>Wrong = 0 |
| | ( b) a known AE becomes serious<br>report as an SAE within 24hrs to the sponsor ( & MCC if it's an investigator driven study), report to ethics as per it's requirements | |
| 5. | Apart from sponsor, who should be notified of an SAE? | 1= Ethics |
| | | 2 = MCC |
| 6 | Have you ever done Ethics application? | |
| | 1.YES | 1 |
| | 2. NO | 2 |
| | | |
| 7. | **Will / do you explain to the patient the procedures involved in the study?** | |
| | Yes | 1 |
| | No | 2 |
| 8 | Will you tell the patient about risks/benefits involved in participating in the particular study?<br>**Please substantiate your answer.** | Yes=1<br>No =2<br>Specify |
| | | |
| 9 | Why should you have 2 copies of informed consents? | |
| | | Pt's copy=1 |
| | | Inv file = 2 |
| 10 | **In your opinion, who should do the Ethics Committee application?** | |
| | Sponsor | 1 |
| | Investigator | GCP req=2 |
| | Unsure | 3 |

**SECTION 5 :**

| | | |
|---|---|---|
| 1. | What is your comment about the following?<br>Reasons for response to be grouped | For/Positive = 1<br>Against = 2 |
| | - Financial Interest Disclosure to MCC & Ethics | |
| | - Placebo-controlled trials | |

| | | |
|---|---|---|
| | - Supply of medication to patients post trial | |
| | The regulatory body (MCC) interest in the number of studies each site is conducting | |
| 2. | Is GCP training given during start-up meetings (**tick the appropriate)** | |
| | Adequate | 1 |
| | Inadequate | 2 |
| | Unsure | 3 |
| | | |
| 3. | Name any 3 factors that affect your GCP implementation in your work place:- specific answers to be grouped | |
| | 1. | |
| | 2. | |
| | 3. | |
| | | |

SECTION 6:

| | | |
|---|---|---|
| 1. | How much time at an average do you spend getting an informed consent? | specify |
| | | |
| 2. | **What are the common reasons that that contribute to the withdrawal of patients from the study?: AE/ side effects/ SAE = 2. 1**<br>Disease progression including reaching of end point= 2.2<br>*Consent withdrawal 2.3*<br>Other = 2.4 (to be grouped and analysed) | |
| | | |
| 3. | **Have you ever heard of Data protection Act / Directive? Please explain** | Yes=1<br>No=2 |
| | **Data is protected. Confidentiality goes according to the informed consent signed. When patient withdraws from the study, his data cannot be used unless it is specified in his informed consent that the data can be used after the patient's withdrawal from the study.** | specify |
| 4. | **What do you tell your patients about the risks of participating in the study?** | |
| | **Answers to be grouped including: painful procedures, side effects, blood tests,** | |
| | **Possibility of getting placebo, frequency of visits: all as per specific trial** | |
| 5. | **Have you read (2000) Dept. of Health GCP Guidelines?** | |
| | **YES** | 1 |
| | **NO** | 2 |
| 6. | **If yes, please identify key provisions: answers to be grouped** | specify |
| | **(a)** | |
| | **(b)** | |
| | **(c )** | |

| | | |
|---|---|---|
| | **(d)** | |
| | **(e)** | |
| 7. | **Do you have any problem in applying these Guidelines?** | |
| | **YES** | 1 |
| | **NO** | 2 |
| | (Please specify) answers to be grouped | |
| 8. | **Have you attended any GCP course before?** | |
| | **1.YES** | 1 |
| | **2. NO** | 2 |
| | **If no, would you like to attend one? If yes = +1, if no = +2, if any reason stated, to be grouped** | |
| | | |
| 9. | **What are the topics that you would like to see covered on a GCP course?** | specify |
| | **Answers to be grouped** | |
| | | |
| 10 | What do you recommend for the sponsor to do, in improving your conduct of clinical trials? | specify |
| | Answers to be grouped | |
| | | |

**THANK YOU FOR YOUR TIME AND ASSISTANCE**

**Annexure 6:**
**SOUTH AFRICA : CLINICAL TRIAL APPLICATION FORM**

**SECTION 1 – CHECK-LIST OF REQUIRED DOCUMENTATION**

*To be completed by Applicants for all Clinical Trials*

## COVER SHEET

**Study Title:**

**Protocol No:**

**Version No:** **Date of Protocol:**

**Study Drug:**

**MCC Ref number (if applicable):**

**MCC Ref number(s) of comparator drug(s) (if applicable):**

**MCC Ref number(s) of concomitant drug(s) (if applicable):**

**Date(s) MCC approval of previous protocol(s):**

**Sponsor:**

**Applicant:**

**Contact Person:**

**Address:**

**Telephone Number:** **Fax Number:**

**Cell Number:**

**E-mail address:**

To be completed by MCC

**Date original application received:**

**Tracking No:**

**Proposed Clinical Trials Committee Meeting Date if applicable:**

**Signature:** **Date:**

**ACKNOWLEDGEMENT OF RECEIPT OF CTA (Contact details to be completed by the applicant). Whole cover sheet to be faxed to applicant once details in block above are completed.**

**Contact Details: Name :** **Fax No.:**

**Receipt of new application is hereby acknowledged.** **Date:**

**Signature (of MCC recipient):** **Name:**

CHECKLIST

| **Applicant's** **MCC** |
|---|

**check list**
**double-check**

**COVERING LETTER** ☐

☐ **FULLY COMPLETED APPLICATION (SECTIONS 1–3)** ☐

☐ **PROTOCOL (INCLUDING RELEVANT QUESTIONNAIRES ETC.)** ☐

☐ **PATIENT INFORMATION LEAFLET(S) AND INFORMED CONSENT(S)** ☐

☐ **INVESTIGATORS BROCHURE AND / OR ALL PACKAGE INSERT(s)** ☐

☐ **INVESTIGATOR'S CV(s) IN MCC FORMAT** ☐

☐ **SIGNED DECLARATION(s) BY INVESTIGATOR(s)** ☐

☐ **REGIONAL MONITOR'S CV AND DECLARATION** ☐

☐ **CERTIFICATE(S) OF ANALYSIS (May be submitted with ethics approval letter)** ☐

☐ **INSURANCE CERTIFICATE** ☐

**AND IF NECESSARY:**

☐ **LETTER ENDORSING GENERIC INSURANCE CERTIFICATE** ☐

☐ **ETHICS APPROVAL**

**OR** ☐

☐ **COPY OF LETTER APPLYING FOR ETHICS COMMITTEE APPROVAL**

☐ **COPY/IES OF RECRUITMENT ADVERTISMENT(s) (IF APPLICABLE)** ☐

☐ **FINANCIAL DECLARATION (SPONSOR AND NATIONAL PI)** ☐

**Electronic versions of the application form (Sections 1 –3), the protocol, the investigator's brochure and/or other relevant documents:**

☐ **LABELLED DISKETTE/CD-ROM (MSWORD OR RICH TEXT FORMAT)** ☐

**List of files submitted on diskette/CD-ROM:**

**NB: DO NOT SUBMIT THE APPLICATION IF DOCUMENTATION IS INCOMPLETE: IT WILL NOT BE PROCESSED**

Declaration by applicant:

We, the undersigned have submitted all requested and required documentation, and have disclosed all information which may influence the approval of this application.

We, the undersigned, agree to ensure that if the above-said clinical trial is approved, it will be conducted according to the submitted protocol and South African legal, ethical and regulatory requirements.

_____ _____

*Applicant (local contact)*

*Date*

_____ _____

National Principal Investigator / *National Co-ordinator /* Other (state designation)

Date

**SECTION 2 – ADMINISTRATIVE AND SUPPLEMENTARY DETAILS**

Title:

Protocol Number/identification:

Date of protocol (initial/final):

**Part 1: CONTACT DETAILS (NAME/ADDRESS/TEL/CELL/FAX/E-MAIL)**

1.1 Applicant: (as in Section 1):

| **Applicant** | **Address** | **Phone** | **Fax** |
|---|---|---|---|
| | | | |

1.2 Sponsor: (as in Section 1):

1.3 If no sponsor – person or organisation initiating, managing, and / or funding the clinical trial

1.4 Local Contact Person for correspondence:

| **Local Contact Person** | **Address** | **Phone** | **Fax** |
|---|---|---|---|
| | | | |

1.5 National Principal Investigator/Coordinator: (or equivalent person):

| **National Coordinator** | **Address** | **Phone** | **Fax** |
|---|---|---|---|
| | | | |

1.6 International Principal Investigator: (if applicable)

1.7 Regional Monitor: (as in Section 1)

Part 2: DETAILS OF INVESTIGATIONAL PRODUCT(s)

**2.1 Name(s) and details of investigational product(s) to be used in trial: [Formulation(s) and strength(s) (e.g. 10 mg/ml–10ml amp.)]**

**Include MCC registration number and date of registration if applicable.**

**Compound name:**

**Formulation:**

**Strength:**

**2.2 Name(s) and details (as above) of comparator product(s) and MCC registration number(s) and date(s) of registration if applicable: [Ensure package inserts or complete pharmacological information been included (Section 1).]**

**2.3 Name(s) and details (as above) of concomitant medication(s) including rescue medications which are required in the protocol, and MCC registration number(s) if applicable: [Ensure package inserts or complete pharmacological information has been included with application (Section 1).]**

2.4 Estimated Quantity of Trial Material (each drug detailed separately) for which exemption will be required:

2.5 If any of the above drugs are available in South Africa, give an explanation for not using what is available in South Africa:

2.6 Details of receiving of drugs from supplier, storage, dispensing, packaging of drugs:

2.7 Date MCC registration applied for – or envisaged date of application for trial medication. Explain if registration is **not** envisaged:

2.8 Registration status of entity, for the indication to be tested in this trial, in other countries: (i.e. Country: date registered / date applied for / date registration refused / date registration withdrawn by applicant / date registration cancelled by regulatory authority) [Attach as an appendix if necessary.]

**<u>Part 3</u>: DETAILS OF TRIALIST(s) AND SITE(s)**

3.1 Details of Investigator(s): [designation, title: (i.e. principal investigators / investigators) Include Name/Address/Tel/Cell/Fax/E-Mail]:

**SITE 01:**

| **Designation** | **Name** | **Address** |
|---|---|---|
| Principal Investigator and National Coordinator | | |
| Sub-investigator | | |
| Sub-investigator | | |
| Sub-investigator | | |
| Sub-investigator | | |

| **Name and E-mail** | **Phone number** | **Fax number** | **Cell** |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

**SITE 02:**

| **Designation** | **Name** | **Address** |
|---|---|---|
| Principal Investigator | | |
| Sub-investigator | | |
| Sub-investigator | | |

| **Name and E-mail** | **Phone number** | **Fax number** | **Cell** |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

**SITE 03:**

| Designation | Name | Address |
|---|---|---|
| Principal Investigator | | |
| Sub-investigator | | |
| Sub-investigator | | |
| Sub-investigator | | |

| Name and E-mail | Phone number | Fax number | Cell |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |



3.2 Current work-load of Investigator(s): (Number of studies currently undertaken by trialist(s) as principal and/or co- or sub-investigator, and the total number of patients represented by these studies. Time-commitments of researcher(s) in relation to clinical trial work *and* non-trial work.)

Recommended format for response: This tabulated format is attached to the investigator CVs for all sites and is completed based on a 60-hour workweek.

| | | |
|---|---|---|
| Investigator (Name and designation): | | |
| Total number of current studies (all stages) on specified date | | |

| | | | |
|---|---|---|---|
| Total number of patients / participants for which responsible on specified date | | | |
| **ESTIMATED TIME PER WEEK [168 hours denominator]** | | **Hours** | **%** |
| ***Clinical trials*** | Clinical work (patient contact) | | |
| | Administrative work | | |
| Organisation (Practice / university / employer) | Clinical work | | |
| | Administrative work | | |
| ***Teaching*** | Preparation / evaluation | | |
| | Lectures / tutorials | | |
| Writing up work for publication / presentation | | | |
| Reading / sourcing information (e.g. internet searches) | | | |
| Other (specify) | After hours on call consultation, work related and community outreach programme | | |

3.3 Details of Site(s) (Name of site, physical address, contact details, contact person, etc.)

| **Name of site and primary contact** | **Physical address** | **Contact details** |
|---|---|---|
| | | |
| | | |
| | | |
| | | |

3.4 Capacity of Site(s): (Number of staff, names, qualifications, experience -- including study co-ordinators, site facilities, emergency facilities, other relevant infrastructure)

**Site 01**

| **Site capacity**<br><br>Number of support staff:<br>Study coordinators and nurses: | | |
|---|---|---|
| **Details for support staff** | | |
| **Name** | **Qualification** | **Experience** |
| | | |
| | | |
| **Other study staff** | | |
| | | |
| | | |
| | | |
| **Overall infrastructure of the site** | | |
| | | |
| **Emergency facilities** | | |
| | | |

**Site 02**

| **Site capacity**<br><br>Number of support staff:<br>Study coordinators and nurses: | | |
|---|---|---|
| **Details for support staff** | | |
| **Name** | **Qualification** | **Experience** |
| | | |
| | | |
| **Other study staff** | | |
| | | |
| **Overall infrastructure of the site** | | |
| | | |
| **Emergency facilities** | | |
| | | |

**<u>Part 4</u>: PARTICIPANTS (SUBJECTS)**

4.1 Number of participants in South Africa:

4.2 Total worldwide:

4.3 Total enrolment in each SA centre: (if competitive enrollment, state minimum and maximum number per site.)

4.4 Volunteer base from which South African participants will be drawn:

4.5 Retrospective data indicating potential of each site to recruit required number of patients within envisaged duration of trial. (SA Guidelines 2000, Item 3.3, p15) [May be attached. Label clearly as 'Section 2 Item 4.5']

**Part 5: OTHER DETAILS**

5.1 If the trial is to be conducted in SA and not in the host country of the applicant / sponsor, provide an explanation:

5.2 Estimated duration of trial:

5.3 Name other Regulatory Authorities to which applications to do this trial have been submitted, but approval has not yet been granted. Include date(s) of application:

5.4 Name other Regulatory Authorities which have approved this trial, date(s) of approval and number of sites per country:

5.5 If applicable, name other Regulatory Authorities or Ethics Committees which have rejected this trial and give reasons for rejection:

5.6 If applicable, details of and reasons for this trial having been halted at any stage by other Regulatory Authorities:

5.7 Details if this trial is being undertaken in SADC, any other country in Africa, or any country where there is no regulatory control of clinical trials:

5.8 Previous studies using this agent which have been approved by MCC:

**MCC approval number:**
Study title:
Protocol number:
Date of approval:
National PI / Principal Investigator:
Date(s) Progress report(s):
Date Final report:

5.9 If any substudies are proposed as part of this protocol, indicate whether or not they will also be done in South Africa. If not, please explain.

*Part 6: ETHICS*

***6.1 Ethics Committee responsible for each site, date of approval or date of application:***

***6.2 Attach copy of response(s) made by, and/or conditions required by ethics committee(s) if available. Ensure that date of EC response is legible.***

***6.3 State which Good Clinical Practice (GCP) guidelines are being followed. (Particular reference to the South African guidelines required):***

6.4 Details of capacity building component of the trial, if any:

6.5 Details of the training of investigators, monitors, study co-ordinators in terms of carrying out this trial and in terms of GCP:

***6.6 Detailed safety and monitoring plan for each site: [May be attached. Label as 'Section 2 Item 6.6']***

***6.7 Details of trial insurance certificate: (e.g. title, protocol, dates, policy #, amount)***

6.8 Details of possible conflict of interest of any person(s)/organisation(s) who/which will be involved in the trial:

***6.9 Remuneration to be received in SA Rands: (Investigators) (Trial participants) (Others) Indicate broad breakdown of costs to be covered by this amount – if applicable. [Note: the CTC recommends a minimum compensation of R50.00 per visit for participants travel and incidental expenses.]***

*Reviewer's comments on Section 2:*

**SECTION 3 – APPLICANT'S REPORT / PRESENTATION**
[Please use Black 12 point Arial Font, using MSWord or rich text format (rtf) for electronic version]

1. Title:

*CTC Reviewer's comment:*

2. Protocol Number/identification:

3. Rationale for study summarised: (Why should this trial be done at all?) Include statement about South African contribution, if any, to the development of this protocol.

*CTC Reviewer's comment:*

4. Background information (**summarised** – **essential** points that apply to this trial) [1-2 sentences max for each point]:
Disease / problem
South African context (e.g. local epidemiology)
Properties of Drug / Entity; hypotheses about mechanism of action, etc.
Pre-clinical findings: (e.g. laboratory / animal / toxicity / mutagenicity)
Clinical findings (e.g. phases; PK; PD; dose-finding; ADRs, NNT/NNH, other)
Systematic review(s) and/or citations per year-group on a Medline search

*CTC Reviewer's comment:*

5. Objectives of study (clearly listed and justified)

*CTC Reviewer's comment:*

6. Study design (clearly described and each component justified) [includes phase, use of placebo, dosages, randomisation, blinding, duration, etc.]

*CTC Reviewer's comment:*

7. Participants: (number of participants; ability to enroll required number within stated time)

*CTC Reviewer's comment:*

8. Eligibility and enrollment: (Inclusion and exclusion criteria listed and justified)

*CTC Reviewer's comment:*

9. Treatment modalities and regimens, drug accountability [clearly explained and justified for all participant groups/arms e.g. in terms of route of administration, dose, etc. Drug accountability clearly described.]

*CTC Reviewer's comment:*

10. Outcome measurements/variables (each clearly stated and justified)

*CTC Reviewer's comment:*

11. Adverse events (prevention, definitions – including causality assignment, recording, reporting, time-lines, action to be taken, all clearly described)

*CTC Reviewer's comment:*

12. Statistical measures:
Determination of sample size correct, clear and justified (with and/or without stratification)
Statistical method(s) and analysis of quantitative measures appropriate, clear and justified
Statistical method(s) and analysis of qualitative measures appropriate, clear and justified
Data processing (how, where, when, who) clearly described and justified. If a SA person will be involved in data processing, please identify that person
Interim analysis envisaged or not (justify) and stopping rules if applicable (explain)

*CTC Reviewer's comment:*

13. Ethical Issues: justification of 'Section 2 part 6' including:

- ***Explanation of which GCP guidelines are or are not being followed – with particular reference to the South African guidelines***
- Comment on choice of investigators (refer to point C of Introduction, page 2 SA Clinical Trials Guidelines 2000)

- Comment on need for, appropriateness of, and relevance of GCP training / updating / for staff involved in this trial
- Comment on capacity building element of trial
- Comment on resources of sites and sponsor
- Comment on monitors and monitoring plan
- Indicate how additional staff (monitors, pharmacists, nursing staff, etc.) will maintain patient confidentiality, follow the protocol, and abide by ethical and regulatory requirements
- Comment on insurance and indemnity measures
- Comment on Patient Information Leaflet and Informed Consent (NB: inclusion of ABPI guidelines; appropriate level of education/English; possible benefits / risks clear; ensuring patient rights; contact names and numbers, as well as MCC details, included)
- Comment on availability and completeness of separate PILs and informed consent forms for any proposed archiving of blood specimens for later research or for genetics research.
- Comment on ethics of the publication policy
- Comment on treatment and/or management of participants and their disease condition(s) after completion of trial
- Comment on ethics committee capacity to monitor site if not a local ethics committee
- Provide an explanation if minimum recommended compensation for participants is not being provided.

*CTC Reviewer's comment:*

### *14. Other relevant information not included above*

E.g. Are references adequate and dates of references current? Are there discrepancies between protocol and IB or package inserts? Are there specific explanation(s) for these discrepancies? Are the explanations for not following the SA 'GCP guidelines' acceptable?
Other comments on this trial.

*CTC Reviewer's comment:*

---

For office use:

*CTC Reviewer's questions and concerns to be considered and/or forwarded to applicant:*

*CTC Reviewer's recommendation:*

*Declaration of conflict of interests by CTC reviewer:*

*CTC recommendation (date):* 1A, 1B, 2, 3, 4, 5

*MCC decision (date):*

| | | | |
|---|---|---|---|
| Investigator (Name and designation): | | | |
| Total number of current studies (all stages) on specified date | Number | Date | |
| Total number of patients / participants for which responsible on specified date | | | |
| **ESTIMATED TIME PER WEEK [168 hours denominator]** | | **Hours** | **%** |
| ***Clinical trials*** | Clinical work (patient contact) | | |
| | Administrative work | | |
| Organisation (Practice / university / employer) | Clinical work | | |
| | Administrative work | | |
| ***Teaching*** | Preparation / evaluation | | |
| | Lectures / tutorials | | |
| Writing up work for publication / presentation | | | |
| Reading / sourcing information (e.g. internet searches) | | | |
| Other (specify) | After hours on call consultation, work related and community outreach programme | 16 | 26.67 |

| | | | |
|---|---|---|---|
| Investigator (Name and designation): | | | |
| Total number of current studies (all stages) on specified date | Number<br><br>4 | Date<br><br>19 Nov 2002 | |
| Total number of patients / participants for which responsible on specified date | Number:e.g approximately 46 patients are seen between 2 investigators, of which dr Potocnik is one<br><br>• 22 are seen six monthly<br>• 18 are seen three monthly<br>• 2 are seen four monthly<br>• 4 are seen three monthly | Date<br><br>19 Nov 2002 | |
| **ESTIMATED TIME PER WEEK [168 hours denominator]** | | **Hours** | **%** |
| ***Clinical trials*** | Clinical work (patient contact) | | |
| | Administrative work | | |
| Organisation (Practice / university / employer) | Clinical work | | |
| | Administrative work | | |
| ***Teaching*** | Preparation / evaluation | | |
| | Lectures / tutorials | | |
| Writing up work for publication / presentation | | | |
| Reading / sourcing information (e.g. internet searches) | | | |
| Other (specify) | After hours on call consultation, work related and community outreach programme | | |

The purpose of the CTA is to assist members of the Clinical Trials Committee to determine the answers to the following questions:

- Does this proposed trial contribute to new knowledge in a scientific way?
- Are all aspects of this proposed trial ethical?
- Can patient safety be assured?
- Should this trial be done in SA?

The application is divided into three sections.

Section 1: A checklist of required documentation. (If the documentation is incomplete, the application will not be further processed.)
Section 2: Administrative and Supplementary Details.
Section 3: Applicant's Report / Presentation

---

Section 1: Use the checklist to ensure that all the necessary documentation has been collated.

The ethics approval can be submitted later – but a copy of the letter of application for an ethics committee to assess the proposed clinical trial must be included.

If the insurance certificate is not specific to the particular protocol, ensure that there is an accompanying letter stating that the insurance does cover this particular protocol.

List the files submitted electronically and their format(s). Ensure that all required documentation is available electronically. This does not include electronic copies of insurance certificate, CVs, declarations, certificates of analysis, ethics approval, recruitment advertisements, etc. Ensure that it is possible for the reviewer to 'copy and paste' from the electronic documents should this be necessary. [Note: If complete information is provided in Section 3 without any inconsistencies or discrepancies between it and the information in the protocol, the investigator's brochure or other documentation, this should not be necessary.]

Section 2: Should be self-explanatory.

Section 3: Applicants are advised to complete this as a report / presentation as if they were reviewing the proposed trial. Apart from the required information about the trial itself, the question 'why' should be asked constantly and the answers provided in the form of a rationale or justification. The reviewers will read all the documentation provided, will double-check the accuracy of the information provided in this section, and will raise unsatisfactorily addressed issues or unanswered questions. Their

recommendation to the CTC / MCC will be based on their ability to answer the four questions above after reading all the documentation and the applicant's report / presentation.

Item 1. Check that the title is accurate and specific (e.g. if a drug being tested is actually an adjuctive treatment, this should be stated in the title). Make sure that no component is left out of the title – e.g. 'phase'.

Item 3. Make sure that the rationale for doing the study is clear. It could be the next logical component in a series of studies (e.g. phase III following phase I or II trial). It could be to test different delivery mechanisms. It could be a 'marketing study'. Try to make sure the answer to the question 'Why should this study be done at all?' is clear and logical.

Item 4. Should be self-explanatory – the important thing is to be brief without losing essential data.

Item 5. State objectives and give rationale for each of them. Ensure that these are scientifically credible. Double check that each objective will in fact be 'analysed' in the statistics section – or else questions must be asked of sponsor / other about why the objective is included without analysis.

Item 6. Summarise study design in one (to two) sentences then justify each component. Show that this study design is the correct scientific one to answer the stated objectives.

Item 7. Provide details of numbers of participants required and why. Justify, using data from section 2, the ability to recruit the required numbers within a certain time period.

Item 8. List the inclusion and exclusion criteria – and justify each of them in a sentence or a half sentence. Pay particular attention to how these criteria may or may not confound or invalidate the objectives of the trial. Ensure that no discrimination against certain groups takes place – or that particular criteria are well justified. (E.g. HIV patients who have developed resistance to all available treatments.)

Item 9. A brief summary of the actual administration of medications. If participants take certain medications at home, or use a patient-diary, ensure that these are described and are not confusing. Ensure that dosage regimens are consistent with recommendations in the investigator's brochure – e.g. dose modifications in cytotoxic therapy.

Item 10. Clear descriptions of outcome measures. If surrogate markers are being used when the drug is intended to decrease mortality, etc., they

should be justified. Ensure that all intended measurements necessary. Ensure that no intended measurements are likely to be of more risk to participants, than they are likely to provide useful information.

Item 11. Indicate how known or likely adverse events will be dealt with. Clearly describe components requested in Section 3.

Item 12. Ensure that all components are adequately addressed. Answer the question, 'Is this the best statistical approach / method for the outcome measures / objectives?' Clearly indicate reasons for doing an interim analysis or for not doing one.

Item 13. Comment on the adequacy of each of the ethics components requested in terms of the proposed trial. Pay special attention to the Patient Information Leaflet and the Informed Consent process / form. Have they been properly modified for SA? Ensure that if any blood specimens are to be archived or kept for genetics research, that this is appropriately addressed in a separate consent form, and that it makes the various ethical aspects of this clear.

Item 14. Any other comments on the proposed trial – including the quality of the protocol, (e.g. well or poorly written / structured; or does it look like it was simply downloaded from a website?); the extent to which the four questions (which the reviewer must answer) can be satisfactorily answered; any other relevant information which the reviewer could take into account in making a recommendation to the CTC / MCC.

**ANNEXURE 7:** Declaration by Principal Investigators

Name:
Title of Trial:
Protocol:
Site:

1. I have read and understood Item 1.5.5 on page 5 and Section 3 (pages 14 – 20) 'Responsibility of The Principal Investigator (PI) and Participating Investigators' of the *Clinical Trials Guidelines of the Department of Health:2000.*

2. I have notified the South African regulatory authority of any aspects of the above guidelines with which I do not / am unable to, comply. (If applicable, this may be attached to this declaration.)

3. I have thoroughly read, understood, and critically analysed (in terms of the South African context) the protocol and all applicable accompanying documentation, including the investigator's brochure, patient information leaflet(s) and informed consent form(s).

4. I will conduct the trial as specified in the protocol.

5. To the best of my knowledge, I have the potential at the site(s) I am responsible for, to recruit the required number of suitable participants within the stipulated time period.

6. I will not commence with the trial before written authorisations from the relevant ethics committee(s) as well as the South African Medicines Control Council (MCC) have been obtained.

7. I will obtain informed consent from all participants or if they are not legally competent, from their legal representatives.

8. I will ensure that every participant (or other involved persons, such as relatives), shall at all times be treated in a dignified manner and with respect.

9. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial.

[*Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her actions.*]*
*Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)

10. I have* / have not (delete as applicable) previously been the principal investigator at a site which has been closed due to failure to comply with Good Clinical Practice. (*Attach details.)

11. I have* / have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details)

12. I will submit all required reports within the stipulated time-frames.

Signature: Date:

Witness: Date:

**ANNEXURE 8:**

Joint Declaration by Sponsor (or representative) and Principal Investigator (or National Principal Investigator) concerning sufficient funds to complete study*

Title:

Protocol:

I, <full name>, representing <sponsor or representative)

And

I, <full name>, Principal Investigator/National Principal Investigator

Hereby declare that sufficient funds have been made available to complete the above-identified study.

Signed Date

SPONSOR (or alternative)
Name
Address
Contact details

Signed Date

PRINCIPAL INVESTIGATOR (or National PI)
Name
Address
Contact details

*Section 4.13, page 26: Clinical Trials Guidelines 2000, Department of Health, South Africa.

**ANNEXURE 9**

Provisional Declaration by Co- and Sub-Investigators and other staff involved in a clinical trial

Name:
Title of Trial:
Protocol:
Principal Investigator's Name:
Site:

Designation:

13. I will carry out my role in the trial as specified in the protocol.

14. I will not commence with my role in the trial before written authorisations from the relevant ethics committee(s) as well as the South African Medicines Control Council (MCC) have been obtained.

15. If applicable to my role in the trial, I will ensure that informed consent has been obtained from all participants or if they are not legally competent, from their legal representatives.

16. I will ensure that every participant (or other involved persons, such as relatives), shall at all times be treated in a dignified manner and with respect.

17. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial.

[*Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her actions.*]*

*Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)

18. I have not previously been involved in a trial which has been closed due to failure to comply with Good Clinical Practice.

19. I will submit all required reports within the stipulated time-frames.

Signature: Date:

Witness: Date:

**ANNEXURE 10:**
Declaration by Regional Monitor

Name:

Title of Trial:
Protocol:

Site:

20. I have read and understood Item 1.5.7 (p5) and Section 5.1 (p30-33) 'The Monitor' of the *Clinical Trials Guidelines of the Department of Health:2000.*

21. I have notified the South African regulatory authority of any aspects of the above guidelines with which I do not / am unable to, comply. (If applicable, this may be attached to this declaration.)

22. I will carry out my responsibilities as specified in the trial protocol and according to the *Clinical Trials Guidelines of the Department of Health:2000.*

23. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial.

[*Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her actions.*]*
*Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)

24. I have* / have not (delete as applicable) previously been the monitor at a site which has been closed due to failure to comply with Good Clinical Practice. (*Attach details.)

25. I have* / have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details)

26. I will submit all required reports within the stipulated time-frames.

Signature: Date:

Witness: Date:

**Annexure 11:**
MCC Format for CVs of Individuals Participating in the Conduct of Clinical Trials in South Africa.

Trial:

Protocol:

Designation: (e.g. National Principal Investigator, Investigator (Principal, Co- or sub-), Study Co-ordinator, Regional Monitor, Local Monitor, Contract Research Affiliate)

1. Personal Details
   Name:
   Work Address:
   Telephone Number:
   Fax Number:
   Cell-phone Number:
   e-mail address:

2. Academic and Professional Qualifications
3. Health Professions Council of South Africa (HPCSA) registration number if applicable (or other health professions body registration particulars if applicable – e.g. Nursing Council)
4. Current personal medical malpractice insurance details [medical and dental practitioners]
5. Relevant related work experience (brief) and current position
6. Participation in clinical trials research in the last three years (title, protocol number, designation) [If multiple trials, only list those with relevance to this application, or in the last year.]
7. Peer-reviewed publications in the past 3 years
8. Date of last GCP training (as a participant or presenter)
9. Any additional relevant information supporting abilities to participate in conducting this trial. [briefly]

Signature:

Standardised wording to be added to PILs:

(Approved by Clinical Trials Committee on 15/07/2002)

If you have questions about this trial you should first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should 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) 323-4474

e-mail: labusa@health.gov.za

**ANNEXURE 12:**

CLINICAL TRIAL PROGRESS REPORT

A**. MEDICINES CONTROL COUNCIL REF NO.**

B**. PRODUCT INFORMATION**

**GENERIC OR CODE NAME OF DRUG**

**TRADE NAME OF DRUG**

C**. SPONSOR COMPANY INFORMATION**

**NAME:**

**Sponsor Name**

**ADDRESS:**

D. **TRIALIST INFORMATION**

**NAME and ADDRESS OF TRIALIST:**

**Phone:**

**Fax:**

**Phone:**

**Fax:**

**E. TRIAL INFORMATION**

**PROTOCOL NUMBER**

**PROTOCOL TITLE**



**A MULTICENTRE RANDOMISED DOUBLE-BLIND PLACECONT**

**PHASE III STUDY OF THE EFFICACY OF…**

**1. OBJECTIVES OF THE TRIAL**

**Primary Objectives:**

**Secondary Objectives:**

**DATE OF APPROVAL**

**DATE TRIAL COMMENCED**

**EXPECTED DATE OF COMPLETION**

**E. PATIENT INFORMATION:**

**NUMBER OF PATIENTS PROPOSED FOR SOUTH AFRICA:**

**NUMBER OF PATIENTS ENTERED IN SOUTH AFRICA:**

**NO OF PATIENTS IN THIS SITE:**

**NUMBER OF PATIENTS COMPLETED:**

**NUMBER OF PATIENTS DISCONTINUED:**

**REASONS FOR DISCONTINUATION:**

**SUMMARY OF ADVERSE EVENTS:**

**SUMMARY OF SERIOUS ADVERSE EVENTS REPORTED**

**F. TRIAL PROGRESS**



_____

**SIGNATURE OF TRIALIST** **DATE**

**Comments if any:**

_____

_____

_____ _____

**CLINICAL RESEARCH ASSOCIATE** **DATE**

**Annexure 13**

**A. PARTICULARS OF THE APPLICANT (i.e. treating medical doctor/pharmacist)**

1. Title: First Names: Surname:

2. Health Professions Council (South Africa) Registration Number:

2. Registered academic qualifications:

3. Registered specialty under which you are currently practicing and treating the patient mentioned named in section C below (e.g. general practitioner, paediatrician, physician, nephrologist, etc.) and designation:

4. Practice Number:

6. Registered Physical Address (where the patient records and/or the medicine may be inspected):

7.Postal Address:

8. Telephone number (office hours): Cellular Phone number:

9.Fax number (office hours):

10. Email address:

11. Signature: Date:

12. Official Stamp:

**B. PARTICULARS OF PERSON, COMPANY, OR INSTITUTION IMPORTING THE UNREGISTERED MEDICINE**

1. Category: Pharmacist Pharmaceutical Manufacturer Pharmaceutical Distributor Pharmaceutical Wholesaler Other: Specify

2. Registered Name of company: **SANOFI- SYNTHELABO (Pty) Ltd.**

3. Registration Number of company: **1996/010381/07**

4. Physical Address (where the medicine and/or patient data may be inspected):

HARROWDENE OFFICE PARK, BLD 4, WESTERN SERVICE ROAD, WOODMEAD

5. Postal Address:

POSTNET SUITE 24, PRIVATE BAG X23, GALLO MANOR, 2052, GAUTENG

6. Contact Person: Title: Mrs. First names: xxx Surname: **xxx**

7. Registered Qualifications: **M.Sc**

8. HPC (S.A.)/Pharmacy Council Registration Number:**012345**

9. Official designation:

10. Telephone number (office hours):**(011) xxxx**

11. Fax number (office hours):**(011) xxxx**

12. Cellular phone number:**082/3 xxxxx**

13. Email address:

## C. PARTICULARS OF THE PATIENT

1. Title: First Names: Surname:

2. Age: Gender: Weight: Height:

3. Occupation:

4. Residential Address:

5. Work or postal Address:

6. Telephone number (office hours):

7. Cellular phone number:

8. Diagnosis (Reason for the application to use unregistered medication; full description including severity, staging and prognosis where applicable)

9. Details of current treatment regimen for the above diagnosis (C No. 8.). Include medicinal, surgical and other treatment.

10. Concomitant disease/s (full description including severity, staging and prognosis where applicable):

11. Current treatment regimen/s for the above concomitant disease/s (C. 10)

12.Please specify which of, and the doses of the above treatment regimens (sections C 9 &12 above) that will be continued together with the unregistered medication.

14. Informed Consent obtained for the use of the unregistered medicine on the patient: Yes or No
Please attach a completed valid informed consent form

## D. PARTICULARS OF THE UNREGISTERED MEDICINE FOR WHICH A SECTION 21 APPLICATION IS BEING MADE

1. Manufacturer:
2. Country of origin: Name of South African Subsidiary:

3. Generic Name:
4. Trade Name:
5. Presentation, formulation and quantity required: (e.g. ampicillin 250mg capsules, 1000 capsules per month for 6 months=6000 capsules)

6. Is the medicine approved & registered for the intended use in other countries, including country of origin? Yes or No

7. Please provide documentary proof of the above (No. 6, e.g. medication leaflet, copy of publication in peer reviewed scientific publication): **Refer to: 1. Summary of product characteristics**
**2. Worldwide registration status previously submitted to MCC**
8. Prescription and planned treatment regimen of the unregistered medicine for the above patient (Section C)
(Dose, frequency, route and duration of administration)

9. Specify known adverse drug reactions (ADRs) to this medication, including interactions with concomitant disease/s and medication/s listed in sections C No.s 11 & 12 above. You may attach an approved official medication leaflet.

10. Clearly outline how you intend preventing, monitoring for and managing the above ADRs

11. Clearly state reasons for not using a similar available registered (in S.A.) medication or treatment regimen for the disease mentioned in section C No. 8 above.

12. Motivation for the use of the unregistered medication (do not repeat the indication and reasons listed in Sections C No. 8 & D No. 11)

13. Have you or any other person or institution applied to the MCC for the use of the same or other unregistered medicine for the same patient in the past? Yes or No If yes, specify and supply the MCC approval number.

14. I hereby certify that:
- the use of this unregistered medication/device is purely for the management of the patient s disease and not research,
- data collected during treatment of the patient with the unregistered medication, may only be used for research after obtaining specific approval from the patient and the MCC, and that the MCC will be supplied with the results (published and unpublished) of such research
- a copy of this application form and consent form will be made available on request to the patient and any registered health care professional who may be involved in the treatment of the above patient.
Signed:(Applicant) Date:

**E. INFORMED CONSENT FORM**

I_____(full names of the patient) voluntarily agree to be treated with a medication, namely_____which is not registered in South Africa, by_____ name of doctor, practice, hospital) for_____ (name of the disease).

I confirm that I have been fully informed and my questions answered by _____(name of applicant, i.e. prescribing doctor) about my disease(for which a section 21 application is being made), its cause, severity, prognosis, available (in South Africa) registered treatment options and the reasons for the current state of my illness and the unregistered medication and application to use a medication that is not registered in S.A., and that:

- the medication is not registered in South Africa and that this implies that the quality, effectiveness and safety of this medication has not been verified by the Medicines Control Council (MCC) of South Africa(S.A.)
- the medication will only be supplied to, and used by and on me once specific approval has been obtained from the MCC of S.A.
- the medication_____ (generic and trade names) is approved for the treatment of _____(my disease) in _____(name of the country from which the medication is to be imported), or (the medication is in an advanced stage of development[at least phase III trial] in South Africa and/ or_____(country of origin) and that its quality, effectiveness and safety are well documented and within legally and scientifically acceptable levels)

- appropriate measures will be taken to prevent, monitor and manage the unwanted effects on me of the unregistered medication
- _____( name of doctor) will comply with all regulations of the MCC, laws(S.A. and foreign) and conditions of approval of use of this unregistered medication and accordingly ensure continued availability and supply of the medication
- use of the unregistered medication on and by me is for managing my disease and not for medical research

- any information collected by_____(name of applicant), his/her employer, successor or any other person other that the MCC or its legal representative, may be used for research purposes upon receipt of specific written separate informed consent from me, my guardian or person responsible for my affairs after my death

- I will be free to stop using the medication at any time and that I will inform my (treating) doctor accordingly.

Full Names of patient/guardian:
Signature of patient/Guardian: Date:
Name of doctor(applicant):
Signature of doctor: Date:

Name of witness:
Signature of witness: Date:

***F. PROGRESS REPORT FORM Date:*** *Initial* *Follow-up* *Final*

**F. 1. Particulars of the Treating Doctor/Pharmacist**

**Title:** **Initials:** **Surname**

Postal Address: Telephone no. Fax No:
Email Address:

## F. 2. Patient Particulars:

Title: Initials: Surname:
Age: Gender: Weight: Height:
Phone No: Cell No:

**F. 3. Particulars of the unregistered Medication**

MCC Section 21 Approval No:

Disease for which the unregistered medicine was used:

Generic Name of the medicine: Trade Name:

Dosage that has been given to the patient: (Amount, Route, Frequency and Duration of administration)

Date of commencement of treatment with unregistered medicine:
Date last used: or ongoing treatment

**F. 4. Outcome of treatment**

**F. 4.1Desired effect** **Therapeutic** **or** **Diagnostic** **or** **Prophylactic, e.g. vaccine**

Excellent Good Satisfactory No effect Not assessed
Brief description/comments:

4.2. Adverse drug reaction(ADR) to the unregistered medication

None or Present
If Present: local or systemic Severity: Mild Moderate Severe
Description of ADR including results of laboratory and/or other investigations and management:

Outcome of ADR: Resolved Ongoing Resulted in disability Resulted in death
Signature of Applicant:

**Annexure 14**

**PRINCIPLES OF GCP**

- Clinical trials should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki. This ensures patients within the trial are protected (Department of Health, 2000; ICH GCP, 1996; Raven, 1993; World Medical Association; 2000).

- Before the initiation of a clinical trial risks and benefits should be weighed and it should be established that the risks do not outnumber the benefits. It is emphasized that the scientific needs should not allow scientists to overlook the benefits. If the risks are more than benefits, the study should not be done. When there are no expected clinical benefits for the subject, the Department of Health (2000) clearly states that this should be explained to the prospective participant. This is more applicable to Phase 1 clinical trials.

- The rights, safety and well-being of patients should prevail over the interest of science and society. Scientists want to explore and increase the knowledge base, and as much as this is important for the country and academic development, it should not jeopardize the safety, rights and well being of patients (Department of Health, 2000; ICH GCP, 1996).

- Available clinical and non-clinical information should be adequate to support the proposed clinical trial. It is one of the regulatory authority's requirements to ensure that the applicant submits proof of safety data before the study gets approved.

- There should always be a scientifically and clinically sound protocol. The protocol acts as a guideline to the trialist on what the clinical trial is all about. In case of uncertainty, the clinical researcher is expected to refer to the protocol to avoid errors

and endangering patients. In South Africa, the investigator or potential trialist signs a Declaration of Intent whereby he / she commits him/herself to abide by the protocol, and conduct the clinical trial in compliance with ICH GCP Guidelines (1996) whilst at the same time taking care of patients in the clinical trial, (see annexure 7,8 & 9 for various categories of investigators).

- The trial should be conducted in compliance with the ethics and regulatory approved protocol. When Ethics and Regulatory authority give approval, they specify the number or version of the protocol they are referring to. The clinical trialist is then expected not to deviate from the approved protocol. In case of a protocol amendment, this cannot be implemented until full approval is obtained (Department of Health, 2000).

- The medical doctor (qualified physician or dentist where appropriate) should take care of the patients. It is expected that during the study, some patients may have adverse events that may be ordinary or serious. It is for this reason that there should be a medical doctor who will be able to care for the patient (Department of Health, 2000; ICH GCP Guidelines, 1996).

- The person conducting the clinical trial should be qualified by education, training and experience. If there is lack of experience, the sponsor should give training and support to the trialists.

- Freely given informed consent should be obtained prior any study procedure. There is no study procedure that should done before the patient signs the consent form.

- Clinical data should be recorded, handled, and stored in a way that can allow interpretation, recording and reporting. There should be a log for delegation of duties.

This will ensure that it is only people that have been authorized to handle data that do so.

- The confidentiality of subjects' records should be maintained at all times and should be in line with the regulatory authority requirements. The subjects should be identified in the Case Report Forms (CRFs) by initials and randomization numbers only. The documents should be kept in lockable cupboards so as to control access to them.
- The investigational products should be manufactured and handled in accordance with good Manufacture Practice (GMP), and should be used according to the protocol. The stock to be used for clinical trials should be labeled so "for clinical trial use only". This should not be mixed with other stock.
- Systems with procedures that ensure the quality of every aspect of the clinical trial should be implemented. This should start from planning of the clinical trial up to the end of the trial (Department of Health, 2000; ICH GCP, 1996).

**Annexure 15**

**The Elements of Informed Consent**

This leads us to the discussion of the elements of the informed consent. All informed consent documents should have the following statements as part of their contents: The informed consent form should clearly state that:

- **The trial involves research**: this is important in a sense that when one decides to participate, one will know and anticipate that since this study involves research, any new information may come out and the same information will have an impact on the registration of the drug under study. This involves exploration of issues that are assumed but need to be confirmed scientifically. The results may need to be published at some stage although they would not reveal any person by name. And the fact that at some stage when new information becomes available, it may interfere with the study progress. This interference may lead to the study being prematurely stopped whilst some participants are still benefiting from the study drug (Dept. of Health, 2000; ICH GCP, 1996).

- **The purpose of the trial**: this should be clearly defined so that when one makes a decision to participate, one should be well informed of the objectives of the study. It is important that the patient understands this and it should be put in layman's language (Dept. of Health, 2000; ICH GCP, 1996).

- **Treatments involved and probability for randomization**: it is important to explain to the potential participant that it will be impossible to include everybody with a particular condition or indication. A sample will be randomly selected to allow each participant to have an equal chance of being selected from the entire population or

sample plate. The types of treatments involved should be clearly specified. Even if there is a placebo that will be used, this should be clearly explained and at the same time the potential participant is given the assurance of his/her safety and the availability of standard or alternative treatment. Usually the investigator does randomization. But there are occasions when this does not happen; instead a central randomization procedure gets followed and the investigator is advised under which treatment arm, the participant should fall. In such instances, the patient should be informed (ICH GCP, 1996).

- **Procedures to be followed**: the participant should be informed of all procedures that will take place starting after the signing of the informed consent. There may be procedures that may be painful or invasive such as putting up an intravenous infusion, doing a gastroscopy for diagnostic procedures, giving injections, taking blood to mention but a few. The participant should know the reason for doing such procedures and the frequency of investigations (Dept. of Health, 2000; ICH GCP, 1996).

- **Subject's responsibilities**: it is difficult for the participant to comply if he/she is not sure of what is expected of her, what is or not allowed to be done whilst on the study. This includes information on what medication can be used whilst on the study. At times there are blood tests that will require the participant to fast when coming for a visit The frequency of visits and the window period within visits is important so that when a patient misses the date he / she should know what is the time frame that can be accommodated before it becomes a protocol violation or the participant gets withdrawn from the study (Dept. of Health, 2000; ICH GCP, 1996).

- **Aspects of the trial that are experimental**: as much as some safety data may be available during the study, the study may have aspects that are not yet proven but are

experimental. The participant should be informed of such and assured of what kind of intervention will be done incase of complications or unexpected results.

- **Risks and benefits**: The risks and benefits should be documented and explained. All expected side effects or adverse events should be clearly specified so that the participant will know when to contact the clinical investigator. Even unexpected events should be clarified, the patient should know that it need not be something related to the drug that should be reported, but any event is of importance and needs to be captured. It should be ensured that when conducting a clinical trial, the risks involved, do not outnumber the benefits (Dept. of Health, 2000; ICH GCP, 1996).

- **Alternative procedures and their possible benefits and risks**: The participant should know that participation is not compulsory. The potential participant should be made aware of alternative treatment that is available in case he /she decides not to participate in the proposed study. The participant should be assured that his or her refusal to participate in the study will not jeopardise the availability of alternative procedures and treatment.

- **Compensation in the event of trial related injury**: In case of any kind of injury due to participation in the study, the participant should be assured of compensation without him/her having to prove that it was due to the study drug. If it involves hospitalisation, neither the participant nor the medical aid scheme should be responsible for payment of hospital costs. In South Africa it is part of the application requirements for both the Regulatory Authority (MCC) and Ethics Committee, to be supplied with an insurance certificate as part of submission documents (Dept. of Health, 2000; ICH GCP, 1996).

- **Any payments that may be involved**: if there is any payment that will be given to the participant, this should be documented and clearly specified and the reason given for

such payment. This includes any gifts that would be provided. These should not be so excessive in such a way, that they lead to indirect coercion.

- **Anticipated expenses**: the anticipated expenses should be clearly stated. The regulatory authorities do not allow the participant to run out of pocket due to participation in the study. The MCC and Ethics Committees put emphasis on payment of traveling / petrol plus parking and food expenses (if the time spent on investigator site is long and would require the participant to buy food).

- **Participation is voluntary**: under no circumstances should the participant be coerced to participate in the research study. If it is felt that the relationship between the particular doctor and the patient will encourage coercion, another doctor involved in the study should handle the informed consent procedure (Declaration of Helsinki, 2000; Dept. of Health, 2000; ICH GCP, 1996).

- **Confidentiality of records**: initials or case record number throughout the study should identify the participant. Even when the results are published, no names are used. The informed consent form should state that the monitor, auditors, IEC and regulatory authority may be granted direct access to the subjects' documents, either for monitoring purposes or for auditing.

- The informed consent form should indicate that **the participant may be prematurely withdrawn** depending on the reasons and in some situations, **the trial** may be prematurely terminated.

- The potential participant should be informed of the **planned number of subjects to be involved in the trial,** both locally and internationally and the reason given for the type and size of the sample.

- **Subject's rights** and the fact that the subject can at any time withdraw from the study without jeopardizing his/ her health and access to alternative treatment, should be explained.

In conclusion, the informed consent should state that a copy of the signed document will be given to the participant or the legal representative (Dept. of Health, 2000; Duant, 2003; ICH GCP, 1996; MRC,1998; Morse et. al. 1995).