A FREQUENCY TREND ANALYSIS OF MAJOR AND CRITICAL AUDIT FINDING GROUPINGS FOR CLINICAL TRIALS INVOLVING CENTRAL NERVOUS SYSTEM STUDIES

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Masters of Science in Medicine in Pharmaceutical Affairs

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DECLARATION

I, Elma Louw, declare that this research report is my own work. It is being submitted for the degree of Masters of Science in Medicine in the branch of Pharmaceutical Affairs in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

_____

_____ day of _____, _____

DEDICATION

To my husband

Thank you for all the support and for making life so much easier when I paid so much attention to the computer.

ABSTRACT

Quality Assurance (QA) Audits are an essential component and an integral part of clinical trials. As a quality improvement tool, forming part of Good Clinical Practice (GCP) an audit can demonstrate that real efforts are being made to improve and enhance the quality of professional care to all trial subjects participating in clinical trials. Specifically, clinical research performed on the central nervous system (CNS) involves distinctive areas of concern to adherence to good clinical practice in this therapeutic area. For example an informed consent process not conducted appropriately for subjects with e.g. Schizophrenia or Alzheimer's disease; or inter-individual rating differences in instances when different investigators (psychiatrist) assess a trial subject. A need was identified to analyze the association between the CNS indication audited and the audit findings and to perform a trend analysis that highlight re-occuring audit findings.

A total of 123 CNS audit reports were obtained from the Quality Assurance Departments of Quintiles in South Africa and Europe. The audit reports were grouped into the 15 CNS indications that were audited. Five hundred and six (506) audit findings were derived from the 123 CNS audits reports. The audit findings were categorized according to GCP subject matter, regulatory requirements or Standard Operating Procedures (SOPs). The severity of audit findings was classified as critical or major.

The results of this investigation suggested a need for substantial improvement in three important areas. Firstly; adherence to the study requirements inclusive of relevant Standard Operating Procedures (SOPs). Secondly the development of better defined protocols and thirdly training of monitors. Study planners and Clinical Trial Management should take a proactive role to minimize the audit findings by ensuring monitors with experience in the research field should be involved in the study. Procedures should be implemented to educate site staff. Focus should be placed on the importance of detailed source documentation, adherence to investigational product dosage requirements, the conduct of the informed consent process, and adequate study documentation maintenance.

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NOMENCLATURE: LIST OF ABBREVIATIONS

CNS	Central Nervous System
CRF	Case Record Form
CRO	Clinical Research Organization
CSV	Computer System Validation
CV	*Curriculum vitae*
FDA, CFR	USA Code of Federal Regulations
GAD	Generalized Anxiety Disorder
GCP	Good Clinical Practice
GLP	Good Laboratory Practice Guideline
ICH GCP	International Conference of Harmonization Good Clinical Practice
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator Site File
MCC	Medicine Control Council
MDD	Major Depressive Disorder
OHRP	Office of Human Research Protection
PHND	Post Herpgic Neuralgia Disorder
PI	Principal Investigator
QA	Quality Assurance
SAE	Serious Adverse Events
SAGCP	Conduct of Clinical Trials in Human Participants in South African
SDV	Source Data Verification
SOP	Standard Operating Procedures
TMF	Trial Master File

NOMENCLATURE: GLOSSARY

Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Adverse Event (AE)

Any untoward medical occurrence in a patient, or clinical investigation subject, administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

Approval (in relation to Institutional Review Boards)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place.

Audit Report

A written evaluation by the sponsor's auditor of the results of the audit.

Audit Trail

Documentation that allows reconstruction of the course of events.

Case Record Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Clinical Trial/Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Comparator (Product)

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Contract Research Organization (CRO)

A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Direct Access

Permission to examine, analyzes, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor’s proprietary information.

Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Impartial Witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization’s (CRO’s) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Investigational Product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Sub investigator.

Investigator / Institution

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

Investigator's Brochure

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Legally Acceptable Representative

An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Monitoring Report

A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

Opinion (in relation to Independent Ethics Committee)

The judgment and/or the advice provided by an Independent Ethics Committee (IEC).

Original Medical Record

See Source Documents.

Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Regulatory Authorities

Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:
results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or
is a congenital anomaly/birth defect

Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

Sub investigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

Subject/Trial Subject

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

Trial Site

The location(s) where trial-related activities are actually conducted.

Vulnerable Subjects

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, and patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

CHAPTER 1

1.0 INTRODUCTION

1.1 What is a Clinical Trial?

A clinical trial is a drug study often, but not always sponsored by a pharmaceutical or biotechnology company. Health-related government agencies could also provide funding for a clinical trial. The purpose of these studies is to find out whether a medication is safe to use and effective against various diseases, indications or medical conditions. In order to study the medication, several questions need to be clarified. For example, what patient population or disease is the drug meant to treat?. What criteria should be used for accepting participants into the study?. What general and disease-specific information are the study doctors going to obtain?[(1)].

1.2 The role of Quality Assurance in Clinical Trials

Societies are increasingly questioning quality of care and concepts of professional discretion or clinical freedom in the conduct of clinical trials. The stark evidence of this shift in attitudes towards clinical trials is shown in the demands of pressure groups, press coverage, calls for public inquiries, and the increase of complaints, legal challenges and claims for redress[(2)].

Investigators, trial participants, sponsors, clinical research organizations (CROs), ethics committees and the wider public all share equally in the need to establish and maintain confidence in the quality of clinical trials performed on human participants. Quality assurance auditing is one of the most important aspects of clinical research that can serve and be used to retain the trust and respect in an increasingly critical environment [(1)].

Audit is not a new process. As early as 1750 BC, King Hammurabi of Babylon instigated audit for clinicians with regard to outcome, sometimes with serious consequences for the clinician both financially, and with regard to life and limb, in the event of poor performance[(3)].

Clinical audit has moved on from these early beginnings, but it was only between 1989 and 1990, that money was first made available to finance the development of audit activity in clinical trials [(3)].

QA audits are performed to assure and to demonstrate that clinical trials are organized and conducted in compliance with the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South African (SAGCP), local regulatory requirements (Medicines Control Council (MCC)), The USA Code of Federal Regulations (FDA; 21CFR parts 50, 54, 56 and 312), OHRP –Office of Human Research Protection, International Conference of Harmonization Good Clinical Practice (ICH GCP), Good Laboratory Practice Guideline (GLP), company policies (either Pharmaceutical or Clinical Research Organization (CRO)) in addition to the written commitments to the sponsor. Thus, it provides additional confidence to the sponsor concerning the validity and accuracy of clinical study data [(4)].

1.3 Type of Audit

Different types of clinical trial audits could be performed, depending on the reason for the audit, the scope of the audit and/or the objective of the audit. For example Trial Master File Audit, Data Management Audit, System Audit and Investigational Site Audit, Laboratory Audits and Drug Manufacturing Audits. For the purpose of this research report the conduct of Trial Master File and Investigator Site Audits are explained in section 1.3.1 and 1.3.2 of this report.

There is no established guideline, which determines the number, type and frequency of an audit that should be conducted per study. The decision should be guided by the quality concerns raised by study team;

- Importance of a study:– major contribution to data, geographical spread,
- New or previously un-audited investigator;
- Significant findings noted during previous audits;
- Data anomalies - e.g. multiple protocol violations;
- Unexpected high incidence of serious adverse events (SAE);
- High or low enrolment of study participants;
- Investigators workload;
- Number of investigational sites per project;
- Phase of the study;
- Time and money allocated for the site audit.

An audit is conducted throughout the course of a “live” study, so any problems can be resolved.

1.3.1 Trial Master File audit

Trial Master Files (TMF) consists of essential study documents. Essential documents are those documents that individually and collectively permit the evaluation of the conduct of the trial and the quality of data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of GCP and with the applicable regulatory requirements. The documents are filed in duplicate i.e. at the investigator site/institution and sponsor office. Filing the essential documents at the investigator site/institution and sponsor office in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor or monitor [(7)].
The purpose of a TMF audit is to ensure that the study team and investigator have maintained all study information according to the protocol and SOPs and in compliance with requirements, guideline and regulations at the office and at the investigator site[(6)].

The following essential study documentation is reviewed during the TMF audits to determine compliance with ICH GCP [(6)], SAGCP [(8)] and 21CFR parts 50, 54, 56 and 312[(9)]

- *Curriculum vitae* (CV) of study personnel to determine qualification and training.
- Signature sheet/responsibility list to verify the delegation of responsibilities.
- Regulatory notification and approval documentation.
- Institutional Review Board (IRB) / Independent Ethics Committee (IEC) submission, notification, acknowledgment and approval documentation.
- Patient Information and Consent Form review of the template consent and subsequent translations or amendments following IRB/IEC review.
- Control, storage, and distribution of investigational product by reviewing all drug dispensing records, drug accountability records, Certificates of Analysis and drug disposition forms.
- Adverse event reporting.
- Protocol compliance through review of site visit reports, source data verification (SDV) documentation, the protocol deviation log and any relevant correspondence.

- Biologic specimen/special test management and handling.
- Case history record keeping.
- Performance of sponsor/CRO responsibilities, including review of visit reports, monitoring frequency and comparison with contractual obligations.
- Retention of essential documents.

The audit may be conducted in conjunction with a planned investigational site audit or separately. If not conducted with a scheduled site audit, the selection of the TMFs to be audited at the office, can be randomly based on any of the following: concerns raised by the monitor or other responsible individuals; Pivotal data – data upon which an application is based; un-audited monitor; significant findings noted during previous audits; funds available; logistical concerns[(5)].

1.3.2 Investigational Site Audit

In keeping with the general principals of GCP, clinical trial auditor and/or company should have written SOPs specifying how site audits will be conducted, how selection of sites will be made, and what format will be used for audit reports[(4)].

After the selection of a particular investigator site for an audit, the auditor shall notify the monitor that an audit will be performed at a selected investigational site. The monitor shall contact the site to inform the principal investigator (PI) or study site coordinator of the audit and schedule proposed audit dates with the investigator [(11)].

An investigational site audit (ISA) is usually preceded by an in-house audit of the TMF. The audit process might be as follows [(3)].

Opening Meeting

An auditor will interview the study team to establish:

- Organization of the study site, and responsibilities delegated by the PI
- Procedures and practices followed when conducting the clinical trial
- Monitor interaction with the clinical investigational team
- Handling of data and Case Record Form (CRF) completion

- Patient population, recruitment and consent procedures
- IRB/IEC procedures
- Investigational product (IP) storage, dispensing and accountability
- Facilities performing laboratory testing

Following the opening meeting, the auditor shall perform the following activities, as appropriate to the objectives of the audit, in order to determine site compliance with applicable regulations, GCP, relevant SOPs and the protocol as warranted:

Tour of the Facilities

- Inspect study-related examination, testing and treatment facilities and equipment, including applicable maintenance and calibration records.
- Inspect investigational product storage and preparation areas, including security provisions and environmental controls.
- Inspect specimen processing and storage areas, if applicable, including relevant processing records and refrigerator/freezer logs.
- Inspect record storage areas.

Review all Informed Consent Forms

- Examine in detail the informed consent documents for participants to ensure:
    - Compliance with ICH GCP[(6)], SAGCP[(8)] and 21CFR parts 50, 54, 56 and 312[(9)]:
    - Correct approved version was used
    - Informed consent forms were properly executed
    - Signed consents were obtained from participants prior to undergoing any protocol required procedures.

Review the Participant Files (inclusive of source notes) and Case Record Forms (CRFs)

- Collect a representative sample (at least three randomized participants) of CRFs and review against source documents;
- Verify key safety and efficacy data experience i.e.
    - serious adverse events,
    - participants withdrawing due to adverse events,
    - participants recruited at different times during the recruitment period,

- participants from different referring sites.

- Determine eligibility of participants
  - data on the condition of subject at the time the subject entered into the clinical study
  - data of exposure of the subject to the test article
  - data on the condition of the subject throughout participation in the investigations
- Determine whether the investigator reported all dropouts, lost to follow-up etc

Review the Investigator Site File (ISF)

The review includes:

- Local regulatory correspondence/approvals
- IRB/IEC correspondence/approvals (inclusive of submissions and approvals) to and from the IRB/IEC and the investigator e.g.:
  - Protocol and amendments
  - Informed consent
  - Advertisement for subject recruitment (if applicable)
  - Periodic reports
- Signed agreement between involved parties
- *CVs*/qualifications to ensure properly trained and qualified
- Delegation of responsibilities list
- Adverse events experiences and unanticipated problems involving risk to human participants
- Randomization list, enrolment log, Serious Adverse Events (SAE) reported by the site,
- Laboratory normal/reference ranges
- Records pertaining to laboratory specimen
- Monitoring trip reports
- Documentation of follow up to non compliances reported in trip reports
- Electronic records/Electronic signature compliance, if applicable.
- Subject enrolment, drop-outs, lost to follow-up, etc
- Study correspondence (e.g., follow up letters to monitoring visits)

Determine if any significant discrepancies exist between this file and Trial Master File through comparison of ISF findings with TMF findings.

Investigational Product (IP) accountability

- Determine whether the dispenser/person that administered the test article was qualified and authorized (Act 101, 1965) [10), (11)]
- Determine accountability procedure for the IP [10), (11)]
- Inspect the storage area
    - IP stored as specified
    - Controlled access to the controlled substance
- Inspect IP return and destruction procedures

Record retention

- Determine who maintains custody of the required records

Electronic Records and Signature (if applicable)

- Determine compliance with 21 CFR part 11.

Review of facilities and equipment

- Equipment validation / calibration
- Equipment maintenance
- Physical security

Debriefing Meeting

- At the end of the site audit, the auditor will meet with the responsible personnel to summarize audit findings and to resolve any misunderstandings or outstanding questions[4].

1.4 Rating of Audit Findings

After an audit was conducted, the auditor usually reviews all findings to determine which are to be reported as non-compliance and/or quality system deficiencies. The auditor(s) ensures that these are documented in a clear, concise manner in an audit report [13].

All findings need to be supported by objective evidence and should be identified with reference to specific requirements of the standard(s) or other related documents against which the audit was conducted [13].

The following approach should be considered when rating findings [13]:

- Identify procedures/activities/documents that are key to the quality of the process to be audited;
- Define a set of quality requirements for each of these activities or items. For example: list of all documents required in a particular file, dosing compliance, core protocol requirements, completed informed consent forms, accuracy of data recording.
- Rate each finding in relation to the defined requirements. Depending on company practice, these findings are sometimes rated according to the severity of the finding: as critical, major and minor findings. Or rank by score as best, median and worst.

1.5 Audit Report

The content of the audit report should reflect the execution of the audit. It must be dated and signed by the auditors and contain the following items, as applicable [13]:

- The scope, and objective of the audit;
- The audit methodology (procedures, activities), the identification of audit team members and auditee representatives, audit dates, identification of the specific organisation audited and adherence to the audit plan;
- Identification of the reference documents against which the audit was conducted;
- Observations/findings
    - Documented clear, concise manner
    - Supported by objective evidence
    - Be identified with reference to specific requirements of the standard(s) against which the audit was conducted
    - Categorized within audit categories
    - Rated according to a severity scale
- Recommendations for corrective and/or preventative actions may be included
- Audit report distribution list

1.6 Rationale of the Study

When performing an audit in a clinical trial numerous audit findings could be identified that could impact adversely on the trial. Similar findings that occur frequently could be considered a trend.
Adverse findings may affect the validity, integrity, reproducibility or the safety of individual patients and regulatory acceptance of the study.

This research project is intended to highlight re-occurring or similar audit findings which are associated with specific indications/diagnosis within CNS studies. Literature review resulted in limited references which could be an indication that minimal research were performed on this topic previously, this strengthens the need for further research in this area.

Since patient safety, compliance to regulatory requirements, ICH guidelines, company policies and cost saving is a requirement for most pharmaceutical companies when conducting clinical trials the outcome of this study will serve three purposes for study planners.

- It will highlight the frequency of specific audit findings, which would enable study planners to implement preventative measures in future trials;
- Clinical Trial Management could use the guide to determine the level of training and specific GCP categories to be emphasized;
- Building preventative procedures and/or activities into the study conduct would save time and money and minimize GCP non-compliance.

1.7 Aims and Objectives

The primary purpose of this study will be to:

- Analyze the categories and severity of audit findings identified in audits conducted on CNS Trials per CNS indication;
- Establish whether there is an association between the CNS indications that have been audited, the category of the audit finding and the severity of the audit finding;
- Perform a trend analysis to identify the re-occurrence of similar audit findings in CNS studies.

CHAPTER 2

2.0 METHODOLOGY

2.1 Data Collection Methodology

A total of 123 CNS audit reports were obtained from retrospective audits conducted by the Quality Assurance Departments of Quintiles in South Africa and Europe between the year 2002 and 2005. These include 105 investigator site audits and 18 trial master file audits.
It was decided to make use of audit reports from the same therapeutic area i.e. Central Nervous System in order to ensure that the complexity of the audits would be the similar.

Audits reports were selected from South Africa and Europe because:

- the same QA audit procedures, criteria and similar set of Standard Operating Procedures (SOPs) were used by Quintiles in SA and Europe from 2000;
- the same QA SMART database is used in SA as in Europe, therefore, there are similar categories for classification of audit findings.

2.1.1 Exclusion Criteria

- Findings from audits conducted by the QA Departments outside the above-mentioned world region i.e. Australia, America and India will not be included in the research project since the database differs from Quintiles SA and Europe;
- Minor audit findings will not be evaluated since the access to the findings is limited;
- Other therapeutic clinical trials will be excluded;
- Other type of audits i.e. System audits, Data Management audits and Clinical Research Organization audits will be excluded;
- Trial data generated before 2000 will not be included in this research project since different QA audit procedures, criteria and SOPs were used by Quintiles in SA and Europe before the year 2000.

Due to a general confidentiality agreement between the client and Quintiles, the name of the client or the name of the drugs investigated, will not be revealed in this report.

2.2 Data Analysis

Initially, the audit findings recorded in the audit reports were consolidated and analyzed according to a three-fold system of categorization. Findings were categorized in terms of the:

- CNS indication that has been audited (refer to section 2.2.1);
- Audit categories according to SMART Database (refer to section 2.2.2);
- Severity as critical or major (refer to section 2.2.3).

The data was analyzed using the software package STATA version 8. Statistical calculations included descriptive statistics using frequencies and percentages. As an example the percentage of major and critical GCP non-compliance findings were categorized, calculated and recorded. Furthermore, the process examined the degree of dependence or association between some of the variables in the data using contingency table analysis.

The contingency table was analyzed by means of a chi-square analysis. In this study the chi-squared test was applied on: the relationships between the audit category and severity rating for findings per indication – examined if severity is dependent or associated with category or not for each indication.
Throughout the analysis a significance level of 5% will be used.

2.2.1 CNS Indications

Indications in which findings were presented have been listed below.

- Alzheimer’s Disease
- Bipolar Disorder
- Cervical Dystonia
- Epilepsy
- Generalised Anxiety Disorder
- Major Depressive Disorder
- Migraine
- Multiple Sclerosis
- Panic Disorder
- Parkinson’s
- Post-herpetic-neuralagia
- Schizophrenia
- Social Phobia
- Spasticity
- Traumatic Brain Injury

2.2.2 Audit Categories

Audit findings recorded in the audit reports were categorized in the following 74 categories as per the QA SMART Database.

- Analysis
- Backup and Recovery
- Clinical Investigator's Brochure
- Clinical Management Plan
- Code break Envelopes
- Coding
- Computer Hardware
- Computer Software
- Computer System Change Control
- Computer System Functional Design
- Computer System Module Testing
- Computer System Physical Design
- Computer System Requirements Specification
- Computer System Source Code
- Computer System Test
- Confidentiality
- Consent
- Contract
- CRF Completion
- Computer System Validation
- Data Edits
- Data Entry Instructions
- Data Handling
- Data Management Plan
- Data Queries
- Database
- Database Access
- Database Change Control
- Database Validation

- Disaster Recovery
- Equipment
- Essential Documents
- Ethics Committee
- Facilities
- Investigational Product
- Investigator Responsibilities
- IT Handbook
- Laboratory
- Laboratory/Biological Samples
- Manual Data Edits
- Monitoring
- Monitoring Management
- No critical or major issues identified
- Procedures and Work Instructions
- Programming Standards
- Project Hand-over
- Project Organisation /Communication
- Protocol and Amendments
- Protocol Violations
- Quality Assurance
- Quality Control
- Quality Management
- Range and Logic checks
- Records Management
- Recruitment and Randomization
- Regulatory
- Report Content
- Resources
- Risk Management
- Safety Reporting
- Security
- Source Data

- Staff
- Statistical Analysis Plan
- Study Design
- Study Documentation
- Sub-contractor Management
- Suppliers
- Support
- Tracking of Project Status
- Training
- Unassigned
- User Acceptance Testing
- Year 2000

2.2.3 Finding Rating as Critical or Major

The severity of audit findings that has been rated as critical or major according to the following Quintiles Quality assurance SOP [15] rating criteria:

Findings rated as critical:

- Threaten scientific, ethical, regulatory or business integrity and could invalidate the acceptability of a study (or part of it) to a sponsor or regulatory body, or invoke regulatory action;
- Seriously challenge the integrity of key efficacy assessment methodology at one or more sites in a study (e.g. gross failure to control the way assessments are performed, no documentation of procedure, inadequate training in performing key assessments, no calibration or quality control checks);
- Seriously challenge the reliability of key efficacy data at one or more sites in a study (e.g. no supporting source data where expected);
- Represent a serious, systematic failure to observe appropriate patient rights (e.g. failure to seek appropriate ethical approval for the study, failure to obtain consent, failure to inform patients of critical safety issues, failure to inform patients of tests undertaken or abuse of patient data);
- Represent a systematic failure in the reporting of critical safety data to the patients, regulatory authorities and/or ethics committees across the study.

- Seriously challenge the viability/accountability of the investigational product at one or more sites in the study.
- Requires immediate and prompt action

Examples of findings rated as critical include:

- The comparator product had been dispensed to the study patients from marketed stock, not intended for clinical trial usage;
- The investigator backdated/altered the date of patient signatures on consent forms;
- Ethics committee approval had not been obtained for the Protocol, yet the study had been conducted at the site.

Findings rated as major:

- Have an impact upon scientific, ethical, regulatory or business integrity and which, if left unattended could become critical;
- Have the potential to escalate into a critical finding as described above;
- Be systematic, or of a magnitude that challenges the integrity of data or methodology applied across multiple patients at a site;
- Represent a significant non-compliance with ICH-GCP, applicable regulatory requirements - including Data Protection requirements, or corporate Standard Operating Procedures;
- Increase the safety risk to subjects;
- Requires timely action.

Examples include:

- Investigational Product (IP) dosing regime, as described in the protocol, was not correctly followed;
- Informed consent not dated by a subject;
- Protocol amendments/revised consent forms had not been submitted to the Ethics Committee for approval.

Minor findings:

- Indicate a potential systematic fault in process, which could lead to major or critical findings if, repeated or escalated

Examples include:

- Discrepancies were identified between the actual number of tablets returned and the number of IP tablets recorded on the IP Accountability Log;
- The investigator dated the informed consent form on behalf of a few subjects in the study;
- Submission and approval documentation did not contain adequate information to determine which version of the informed consent was approved.

CHAPTER 3

3.0 RESULTS

3.1 Audit Reports Analysis

A total of 123 audit reports from Europe and South Africa were obtained which resulted in the assessment of 15 Central Nervous System (CNS) Indications. A total of 106 Audit reports were obtained from Europe and 17 audit reports from South Africa.

Table 3.1 summarized the type of audit conducted and reports obtained per region per indication.

Table 3.1 List of type of audit reports per region per indication

Indication	**Europe**		**South Africa**		**Total**
	***ISA**	****TMF**	***ISA**	****TMF**	
Alzheimer's Disease	1		1		2
Bipolar Disorder	2	3			5
Cervical Dystonia	1				1
Epilepsy	6		1	1	8
GAD	18		1	1	20
MDD	10	1	5	2	18
Migraine	2	3			5
Multiple Sclerosis	2	1			3
Panic Disorder	8		1		9
Parkinson's	4	1		1	6
PHND	2				2
Schizophrenia	10	1		1	12
Social Phobia	18		1	1	20
Spasticity	1				1
Traumatic Brain Injury	10	1			11
Total	**95**	**11**	**10**	**7**	**123**

*ISA: Investigational Site Audit **TMF: Trial Master File Audit

A total of 506 audit findings were derived from the 123 audit reports. A total of 458 audit findings related to investigational site audits reports i.e. 407 (91.47%)) audit findings from Europe and 51 (83.61 %) from South Africa. A total of 48 (9.49%) audit findings were identified from trial master file audits performed in Europe (38 (8.54%)) and South Africa (10 (16.39%)).

Table 3.2 indicates the number of audit findings obtained per type of audit per region.

Table 3.2 Percentage and frequency of audit findings per type of audit per region

Type of Audit	**Region**		**Total**
	Europe	**South Africa**	
Investigational Site	407	51	458
%	91.46	83.61	90.51
Trial Master File	38	10	48
%	8.54	16.39	9.49
Total	**445**	**61**	**506**
	100.00	**100.00**	**100.00**

From the 123 audit reports a total of 506 audit findings were reported for the 15 indications that were assessed.

Table 3.3 reflects the frequency and percentage of audit findings obtained per region per indication.

Table 3.3 Frequency and percentage of audit findings per indication per region

Indication	Europe	South Africa	Total
Alzheimer's Disease	3	0	3
%	0.67	0.00	0.59
Bipolar Disorder	8	0	8
%	1.80	0.00	1.58
Cervical Dystonia	6	0	6
%	1.35	0.00	1.19
Epilepsy	20	3	23
%	4.49	4.92	4.55
GAD	39	2	41
%	**8.76**	3.28	8.10
MDD	58	45	103
%	**13.03**	**73.77**	20.36
Migraine	22	0	22
%	4.94	0.00	4.35
Multiple Sclerosis	31	0	31
%	6.97	0.00	6.13
Panic Disorder	33	0	33
%	7.42	0.00	6.52
Parkinson's Disease	10	0	10
%	2.25	0.00	1.98
PHND	10	0	10
%	2.25	0.00	1.98
Schizophrenia	45	5	50
%	**10.11**	8.20	9.88
Social Phobia	127	6	133
%	**28.54**	**9.84**	26.28
Spasticity	3	0	3
%	0.67	0.00	0.59
Traumatic Brain Injury	30	0	30
%	6.74	0.00	5.93
Total	**445**	**61**	**506**
	100.00	**100.00**	**100.00**

3.2 Severity Analysis

Table 3.4 summarizes the total percentage of the 506 audit findings, which were rated as major or critical, within the CNS Therapeutic area. Refer to Appendix A (page 47) for a detail rating analysis of audit finding as categorized per indication.

Table 3.4 Severity ratings per indication

Indication	Severity				Total	
	Major		Critical			
	Freq.	**%**	**Freq.**	**%**	**Freq.**	**%**
Alzheimer's Disease	3	0.64%	0	0.00%	3	0.59%
Bipolar Disorder	8	1.69%	0	0.00%	8	1.58%
Cervical Dystonia	6	1.27%	0	0.00%	6	1.19%
Epilepsy	19	4.03%	4	11.76%	23	4.55%
GAD	41	**8.69%**	0	0.00%	41	8.10%
MDD	95	**20.13%**	8	**23.53%**	103	20.36%
Migraine	18	3.81%	4	11.76%	22	4.35%
Multiple Sclerosis	29	6.14%	2	5.88%	31	6.13%
Panic Disorder	33	**6.99%**	0	0.00%	33	6.52%
Parkinson's	10	2.12%	0	0.00%	10	1.98%
PHND	10	2.12%	0	0.00%	10	1.98%
Schizophrenia	37	**7.84%**	13	**38.24%**	50	9.88%
Social Phobia	131	**27.75%**	2	5.88%	133	26.28%
Spasticity	3	0.64%	0	0.00%	3	0.59%
Traumatic Brain Injury	29	6.14%	1	2.94%	30	5.93%
Total	**472**	**100.00%**	**34**	**100.00%**	**506**	**100.00%**

Table 3.5 -3.11 summarize the indications with audit findings rated as major and critical within a specific category.

Table 3.5 Severity analysis per audit category for Epilepsy

Category	Severity		Total
	Major	**Critical**	
Code break Envelopes	1	0	1
%	5.26	0.00	4.35
Consent	2	1	3
%	10.53	**25.00**	13.04
IP	3	1	4
%	**15.79**	**25.00**	17.39
Investigator Responsibility	3	0	3
%	**15.79**	0.00	13.04
Laboratory/Biological Samples	1	0	1
%	5.26	0.00	4.35
Monitoring	1	0	1
%	5.26	0.00	4.35
Monitoring Management	1	0	1
%	5.26	0.00	4.35
Protocol Violations	1	0	1
%	5.26	0.00	4.35
Protocol and Amendments	1	1	2
%	5.26	**25.00**	8.70
Safety Reporting	2	1	3
%	10.53	**25.00**	13.04
Source Data	1	0	1
%	5.26	0.00	4.35
Study Documentation	1	0	1
%	5.26	0.00	4.35
Training	1	0	1
%	5.26	0.00	4.35
Total	**19**	**4**	**23**
	100.00	**100.00**	**100.00**

Bold: Highest percentage results per category

Table 3.6 Severity analysis per audit category for Major Depressive Disorder

Category	Severity		Total
	Major	**Critical**	
CRF Completion	4	0	4
%	4.21	0.00	3.88
Clinical Management Plan	1	0	1
%	1.05	0.00	0.97
Code break Envelopes	1	0	1
%	1.05	0.00	0.97
Confidentiality	1	0	1
%	1.05	0.00	0.97
Consent	7	0	7
%	**7.37**	0.00	6.80
Contract	2	0	2
%	2.11	0.00	1.94
Ethics Committee	10	0	10
%	**10.53**	0.00	9.71
IP	6	1	7
%	**6.32**	**12.50**	6.80
Investigator Responsibility	5	0	5
%	5.26	0.00	4.85
Laboratory/Biological Samples	5	1	6
%	5.26	**12.50**	5.83
Monitoring	7	3	10
%	**7.37**	**37.50**	9.71
Monitoring Management	5	0	5
%	5.26	0.00	4.85
Procedures/Work Instruction	1	1	2
%	1.05	**12.50**	1.94
Protocol Violations	4	0	4
%	4.21	0.00	3.88

Table 3.6 Severity analysis per audit category for Major Depressive Disorder

Category	Severity		Total
	Major	**Critical**	
Protocol and Amendment	2	0	2
%	2.11	0.00	1.94
Quality Assurance	1	0	1
%	1.05	0.00	0.97
Records Management	1	0	1
%	1.05	0.00	0.97
Regulatory	1	0	1
%	1.05	0.00	0.97
Source Data	14	1	15
%	**14.74**	**12.50**	14.56
Study Documentation	12	1	13
%	**12.63**	**12.50**	12.62
Safety Reporting	4	0	4
%	4.21	0.00	3.88
Training	1	0	1
%	1.05	0.00	0.97
Total	**95**	**8**	**103**
	100.00	**100.00**	**100.00**

Bold: Highest percentage results per category

Table 3.7 Severity analysis per audit category for Migraine

Category	Severity		Total
	Major	**Critical**	
Consent	0	1	1
%	0.00	25.00	4.55
Contract	3	0	3
%	**16.67**	0.00	13.64
Ethics Committee	0	2	2
%	0.00	**50.00**	9.09
Investigational Product	1	0	1
%	5.56	0.00	4.55
Monitoring	1	1	2
%	5.56	25.00	9.09
Procedures/Work Instruction	1	0	1
%	5.56	0.00	4.55
Protocol Violations	5	0	5
%	**27.78**	0.00	22.73
Records Management	2	0	2
%	11.11	0.00	9.09
Source Data	2	0	2
%	11.11	0.00	9.09
Study Documentation	2	0	2
%	11.11	0.00	9.09
Training	1	0	1
%	5.56	0.00	4.55
Total	**18**	**4**	**22**
	100.00	**100.00**	**100.00**

Bold: Highest percentage results per category

Table 3.8 Severity analysis per audit category for Multiple Sclerosis

Category	Severity		Total
	Major	Critical	
CRF Completion	1	0	1
%	3.45	0.00	3.23
Consent	5	0	5
%	**17.24**	0.00	16.13
IP	5	1	6
%	**17.24**	**50.00**	19.35
Investigator Responsibility	1	0	1
%	3.45	0.00	3.23
Monitoring	2	0	2
%	6.90	0.00	6.45
Monitoring Management	1	0	1
%	3.45	0.00	3.23
Records Management	1	0	1
%	3.45	0.00	3.23
Regulatory	2	0	2
%	6.90	0.00	6.45
Safety Reporting	4	0	4
%	**13.79**	0.00	12.90
Source Data	1	1	2
%	3.45	**50.00**	6.45
Study Documentation	6	0	6
%	**20.69**	0.00	19.35
Total	**29**	**2**	**31**
	100.00	**100.00**	**100.00**

Bold: Highest percentage results per category

Table 3.9 Severity analysis per audit category for Schizophrenia

Category	Severity		Total
	Major	Critical	
Clinical Management P	2	0	2
%	5.41	0.00	4.00
Code break Envelopes	1	0	1
%	2.70	0.00	2.00
Consent	2	1	3
%	5.41	7.69	6.00
Ethics Committee	2	1	3
%	5.41	7.69	6.00
IP	4	4	8
%	**10.81**	**30.77**	16.00
Investigator Responsibility	4	2	6
%	**10.81**	**15.38**	12.00
Monitoring	3	1	4
%	8.11	7.69	8.00
Monitoring Management	1	0	1
%	2.70	0.00	2.00
Procedures/Work Instruction	1	0	1
%	2.70	0.00	2.00
Protocol Violations	4	0	4
%	**10.81**	0.00	8.00
Protocol and Amendment	1	0	1
%	2.70	0.00	2.00
Quality Management	0	1	1
%	0.00	7.69	2.00
Regulatory	1	0	1
%	2.70	0.00	2.00
Resources	1	0	1
%	2.70	0.00	2.00
Safety Reporting	2	0	2
%	5.41	0.00	4.00

Bold: Highest percentage results per category

Table 3.9 Severity analysis per audit category for Schizophrenia

Category	Severity		Total
	Major	**Critical**	
Source Data	2	3	5
%	5.41	**23.08**	10.00
Study Documentation	4	0	4
%	**10.81**	0.00	8.00
Training	2	0	2
%	5.41	0.00	4.00
Total	**37**	**13**	**50**
	100.00	**100.00**	**100.00**

Bold: Highest percentage results per category

Table 3.10 Severity analysis per audit category for Social Phobia

Category	Severity		Total
	Major	**Critical**	
CRF Completion	2	0	2
%	1.53	0.00	1.50
Consent	11	0	11
%	**8.40**	0.00	8.27
Contract	1	0	1
%	0.76	0.00	0.75
Essential Documents	1	0	1
%	0.76	0.00	0.75
Ethics Committee	4	0	4
%	3.05	0.00	3.01
Investigational Product	18	0	18
%	**13.74**	0.00	13.53
Investigator Responsibility	3	0	3
%	2.29	0.00	2.26
Laboratory/Biological Samples	6	0	6
%	4.58	0.00	4.51
Monitoring	7	1	8
%	5.34	**50.00**	6.02
Monitoring Management	3	0	3
%	2.29	0.00	2.26
Procedures/Work Instructions	1	0	1
%	0.76	0.00	0.75
Protocol Violations	24	0	24
%	**18.32**	0.00	18.05
Protocol and Amendment	3	0	3
%	2.29	0.00	2.26
Records Management	1	0	1
%	0.76	0.00	0.75
Recruitment/Randomization	2	0	2
%	1.53	0.00	1.50

Table 3.10 Severity analysis per audit category for Social Phobia

Category	Severity		Total
	Major	**Critical**	
Safety Reporting	2	0	2
%	1.53	0.00	1.50
Source Data	30	1	31
%	**22.90**	**50.00**	23.31
Study Documentation	12	0	12
%	**9.16**	0.00	9.02
Total	**131**	**2**	**133**
	100.00	**100.00**	**100.00**

Bold: Highest percentage results per category

Table 3.11 Severity analysis per audit category for Traumatic Brain Injury

Category	**Severity**		**Total**
	Major	**Critical**	
CRF Completion	1	0	1
%	3.45	0.00	3.33
CSV	1	0	1
%	3.45	0.00	3.33
Consent	5	1	6
%	**17.24**	100.00	20.00
Contract	1	0	1
%	3.45	0.00	3.33
IP	3	0	3
%	10.34	0.00	10.00
Laboratory/Biological Samples	4	0	4
%	**13.79**	0.00	13.33
Monitoring	1	0	1
%	3.45	0.00	3.33
Records Management	1	0	1
%	3.45	0.00	3.33
Recruitment/Randomization	1	0	1
%	3.45	0.00	3.33
Safety Reporting	5	0	5
%	**17.24**	0.00	16.67
Source Data	3	0	3
%	10.34	0.00	10.00
Study Documentation	2	0	2
%	6.90	0.00	6.67
Training	1	0	1
%	3.45	0.00	3.33
Total	**29**	**1**	**30**
	100.00	**100.00**	**100.00**

Bold: Highest percentage results per category

Figure 3.1 includes a bar chart of the information listed in table 3.4 (page 20) to serve as a graphic representation of the difference in the percentage of audit findings rated as major or critical for each indication.

Figure 3.1 Severity of audit findings within the CNS Therapeutic Area

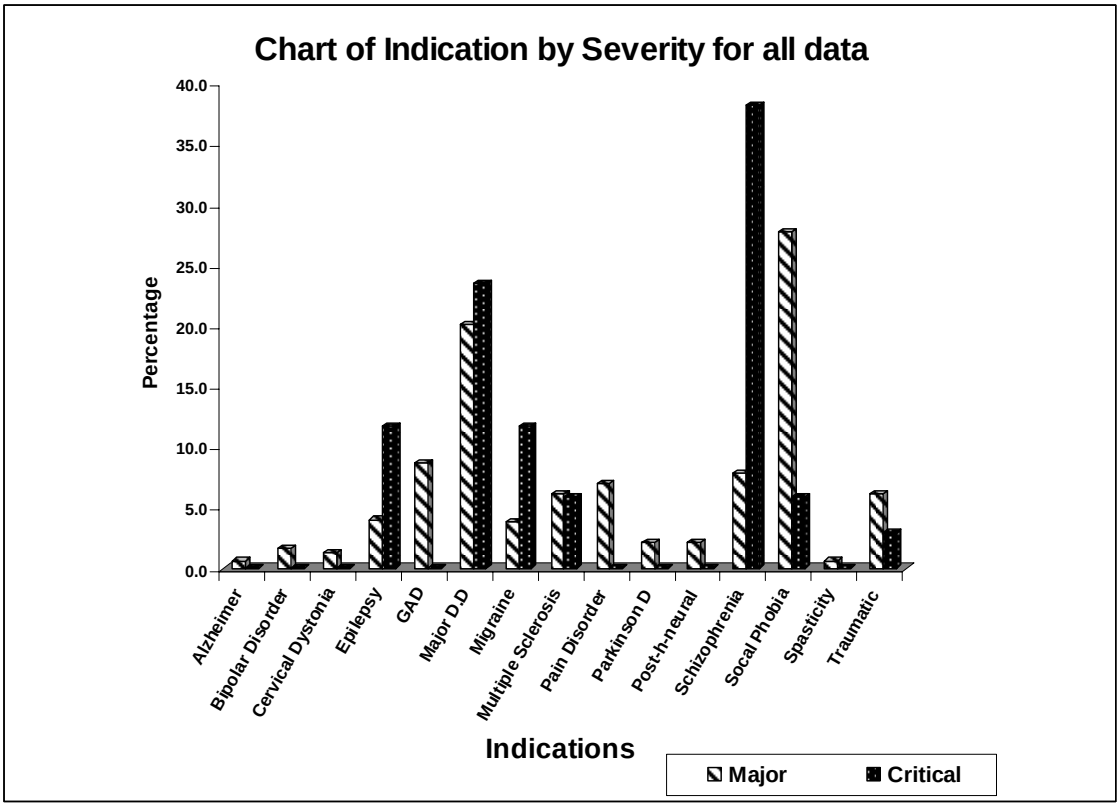


Figure 3.2 and figure 3.3 serve as graphic representations of the percentage audit findings rated as major or critical for each indication per region.

Figure 3.2 Indications by Severity for Europe

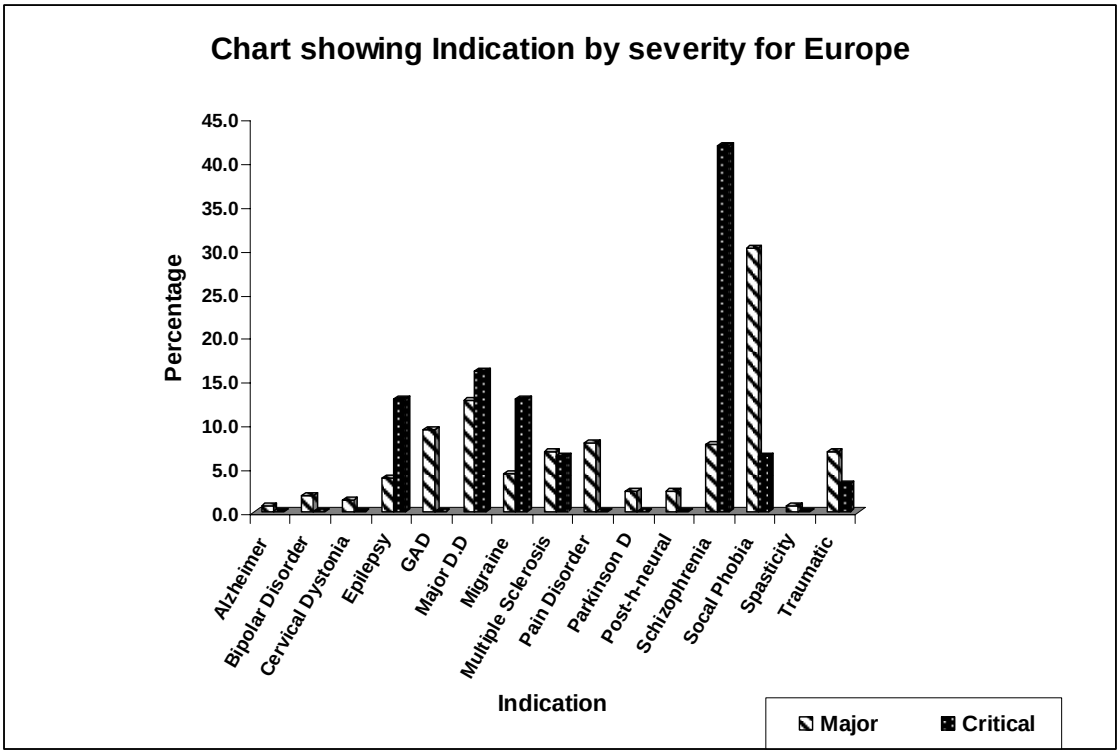
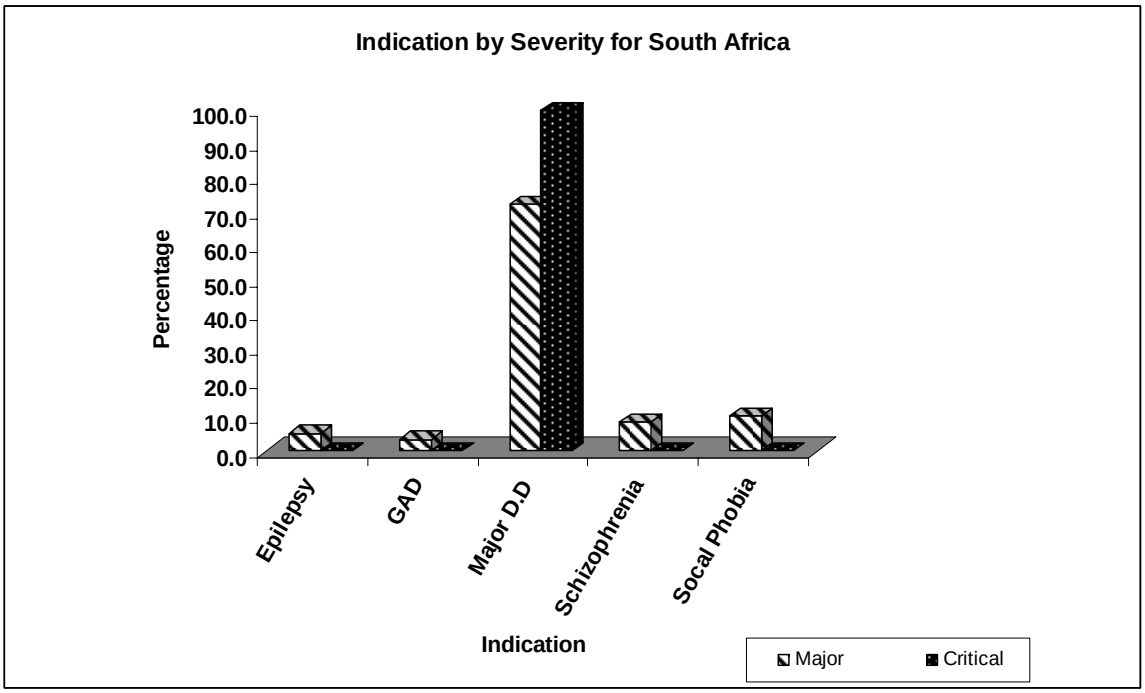


Figure 3.3 Indications by Severity for South Africa



3.3 Trend Analysis

Table 3.12 highlights the frequency and percentage of audit findings within an audit category. Refer to Appendix B (page 68) for a detail listing of re-occurring audit findings as categorized.

Table 3.12 Frequency and percentage of audit findings per category

Category	Frequency	Percentage	Cumulative
Analysis	1	0.20	0.20
CSV	1	0.20	0.40
Case Record Form Completion	12	2.37	2.77
Clinical Management Plan	4	0.79	3.56
Codebreak Envelopes	5	0.99	4.55
Confidentiality	1	0.20	4.74
Consent	46	**9.09**	13.83
Contract	9	1.78	15.61
Essential Documents	1	0.20	15.81
Ethics Committee	28	5.53	21.34
Facilities	2	0.40	21.74
Investigational Product	64	**12.65**	34.39
Investigator Responsibilities	24	4.74	39.13
Laboratory/Biological Samples	20	3.95	43.08
Monitoring	37	**7.31**	50.40
Monitoring Management	12	2.37	52.77
Procedures and Work Instructions	7	1.38	54.15
Protocol Violations	41	**8.10**	62.25
Protocol and Amendments	10	1.98	64.23
Quality Assurance	1	0.20	64.43
Quality Management	1	0.20	64.62
Records Management	6	1.19	65.81

Table 3.12 Frequency and percentage of audit findings per category

Category	Frequency	Percentage	Cumulative
Recruitment and Randomization	3	0.59	66.40
Regulatory	4	0.79	67.19
Resources	1	0.20	67.39
Safety Reporting	24	4.74	72.13
Source Data	85	**16.80**	88.93
Study Documentation	48	**9.49**	98.42
Training	7	1.38	99.80
Unassigned	1	0.20	67.39
Total	**506**	**100.00**	

Bold: Highest percentage results per category

Table 3.13 highlights the frequency and percentage of the 506 audit findings within a category per region.

Table 3.13 Frequency and percentage of audit findings per category per region

Category	Region		Total
	Europe	South Africa	
Analysis	1	0	1
%	0.22	0.00	0.20
CSV	1	0	1
%	0.22	0.00	0.20
Case Record Form	11	1	12
%	2.47	1.64	2.37
Clinical Management Plan	3	1	4
%	0.67	1.64	0.79
Code break Envelopes	4	1	5
%	0.90	1.64	0.99
Confidentiality	0	1	1
%	0.00	1.64	0.20
Consent	41	5	46
%	**9.21**	**8.20**	9.09

Table 3.13 Frequency and percentage of audit findings per category per region

Category	Region		Total
	Europe	South Africa	
Contract	9	0	9
%	2.02	0.00	1.78
Essential Documents	1	0	1
%	0.22	0.00	0.20
Ethics Committee	24	4	28
%	5.39	6.56	5.53
Facilities	2	0	2
%	0.45	0.00	0.40
IP	56	8	64
%	**12.58**	**13.11**	12.65
Investigator Responsibility	21	3	24
%	4.72	4.92	4.74
Laboratory/Biological Samples	17	3	20
%	3.82	4.92	3.95
Monitoring	37	0	37
%	**8.31**	0.00	7.31
Monitoring Management	10	2	12
%	2.25	3.28	2.37
Procedure/Work Instruction	6	1	7
%	1.35	1.64	1.38
Protocol Violations	38	3	41
%	**8.54**	**4.92**	8.10
Protocol and Amendment	8	2	10
%	1.80	3.28	1.98
Quality Assurance	0	1	1
%	0.00	1.64	0.20
Quality Management	1	0	1
%	0.22	0.00	0.20
Records Management	4	2	6
%	0.90	3.28	1.19
Recruitment / Randomization	3	0	3

Table 3.13 Frequency and percentage of audit findings per category per region

Category	Region		Total
	Europe	South Africa	
%	0.67	0.00	0.59
Regulatory	3	1	4
%	0.67	1.64	0.79
Resources	0	1	1
%	0.00	1.64	0.20
Safety Reporting	20	4	24
%	4.49	6.56	4.74
Source Data	76	9	85
%	**17.08**	**14.75**	16.80
Study Documentation	41	7	48
%	**9.21**	**11.48**	9.49
Training	6	1	7
%	1.35	1.64	1.38
Unassigned	1	0	1
%	0.22	0.00	0.20
Total	**445**	**61**	**506**
	100.00	**100.00**	**100.00**

Bold: Highest percentage results per category

3.4 Testing Association

Table 3.14 reflects the evaluation to identify associations between the audit category and severity rating for findings obtained from Europe considering each indication

Table 3.14 Testing association per indication for Europe

Indication	Pearson Chi-squares	Degrees of Freedom	Probability	Conclusion
Alzheimer's Disease	*NA	-	-	-
Bipolar Disorder	*NA	-	-	-
Cervical Dystonia	*NA	-	-	-
Epilepsy	8.541	12	0.741	Not significant
GAD	*NA	-	-	-
MDD	24.997	16	0.070	Not significant
Migraine	18.638	10	0.045	Significant
Multiple Sclerosis	8.908	10	0.541	Not Significant
Panic Disorder	*NA	-	-	-
Parkinson's	*NA	-	-	-
PHND	*NA	-	-	-
Schizophrenia	13.602	15	0.556	Not significant
Social Phobia	8.183	16	0.943	Not significant
Spasticity	*NA	-	-	-
Traumatic Brain Injury	4.138	12	0.981	Not significant

*Not applicable (NA): Only one category (Major) was available and test could not be performed.

Hypothesis: The null hypothesis being tested is that there is no association between category and severity for the indication under consideration.

For Migraine; the results showed significance which implies that there is association between the category and severity. For the other indications, there was no evidence to show that severity is dependent on category of indications.

Table 3.15 reflects the evaluation if the audit category is associated with severity for data obtained from South Africa considering each Indication

Table 3.15 Testing association per indication for South Africa

Indication	Pearson Chi-squares	Degrees of Freedom	Probability	Conclusion
Epilepsy	*NA	-	-	-
GAD	*NA	-	-	-
MDD	18.08	18	0.450	Not significant
Schizophrenia	*NA	-	-	-
Social Phobia	*NA	-	-	-

*Not applicable (NA): Only one category (Major) was available and test could not be performed.

Testing associations could not be performed for the following indications in South Africa since no audits were performed: Bipolar Disorder, Cervical Dystonia, Migraine, Multiple Sclerosis, Post-herpetic-neuralgia, Spasticity, and Traumatic Brain Injury. Refer to table 3.1 (List of type of audit reports per region per indication, 17).

Hypothesis: The null hypothesis being tested is that there is no association between category and severity for the indication under consideration.

CHAPTER 4

4.0 DISCUSSION AND CONCLUSIONS

4.1 Audit Results

It is evident from the table 3.3 (Frequency and percentage of audit findings per region; page 20) that the most prominent indication with highest percentage of findings is Social Phobia which accounts for 26.3%. This indication also has the highest percentage of audit findings in Europe i.e. 28. 5%. The second highest amount of audit findings related to Major Depressive Disorder that accounts for 20.4%. This indication accounts for the highest amount of audit findings in South Africa i.e. 73.8 %. The lowest is Spasticity and Alzheimer's disease which accounts for 0.6% each respectively.

Table 3.4 (Severity ratings per indication; page 21) shows that eight (8) of the fifteen (15) indications investigated have audit findings rated as critical and major. This is Epilepsy, Major Depressive Disorder, Migraine, Multiple Sclerosis, Schizophrenia, Social Phobia and Traumatic Brain Injury. The highest frequency of critical findings was for Schizophrenia i.e. thirteen (38.2%). Second highest was for Major Depressive Disorder i.e. eight (23.5%) critical audit findings. Refer to Appendix A (Audit finding analysis per indication, page 48) for a complete listing of severity rating of individual audit findings per indication. Social Phobia had the highest percentage (27.8%) of major audit findings. The second highest percentage (20.1%) of major audit findings was once again for Major Depressive Disorder.

From the fifteen (15) Central Nervous System (CNS) indications investigated only eight indications were audited in South Africa i.e. Alzheimer's Disease, Epilepsy, Generalized Anxiety Disorder, Major Depressive Disorder, Panic Disorder, Parkinson's, Schizophrenia, Social Phobia (table 3.1, Summary of type of audit reports obtained per region per indication, page 18). It is interesting to note that no major or critical audit findings were identified for Alzheimer, Panic Disorder and Parkinson's disease as opposed to data obtained from Europe. Refer to table 3.3 (Frequency and percentage of audit findings per indication per region, page 20) and figure 3.3. (Indication by severity for South Africa, page 33).

4.2 Re-occurring Audit Findings per Category

From the 74 audit categories as per SMART database (page 13), 506 audit findings were categorized into 29 audit categories (Table 3.12; Frequency and percentage of audit findings per category; page 34). No audit findings were identified for the remainder of the 45 non-compliance categories. The reason for this might be that audit findings relating to these categories would be applicable to different type of audits i.e. data management audits, system audits, not included in this analysis as reflected in table 3.2 (Percentage and frequency of audit findings per type of audit per region; page 19).

From table 3.13 (Frequency and percentage of audit findings per category per region; page 35); no audit findings were identified within the following categories for South Africa i.e. contracts, essential documents, facilities, monitoring, quality management, recruitment and randomization.

It is clear from table 3.12 (frequency and percentage of audit findings per category, page 34) the highest frequency of audit findings i.e. eighty-five (85) was reported for deficiencies noted in the non-compliance category relating to source data (16.80%). The second most prevalent audit findings related to Investigational Product (12.65%). The audit category, study documentation reflects the third most audit findings (9.49%). Forty-six audit findings were identified in the non-compliance category consent (9.09%). The level of results is similar for South Africa and Europe (Table 3.13; Frequency and percentage of audit findings per category per region; page 35). The percentage of protocol violations in Europe (8.54%) is twice the percentage identified in South Africa (4.92%). This category represents fifth highest result level for both Europe and South Africa.

Re-occurring audit findings per category are listed in Appendix B (page 68).

4.2.1 Source Data

Questionable source data [#] could have a critical effect on the authentic reporting of data to the sponsor. Unreliable source data cannot substantiate the integrity of the trial data that have been collected and submitted to regulatory authorities for approval of an Investigational Product. Insufficient source data result in protocol violations and protocol non-compliance. This was confirmed through further analysis of the frequency and type of audit findings in the non-compliance category of *protocol violations* which represents the fifth category with most audit findings (41 audit findings).

The majority of audit findings were from this section. Most of the audit findings related to information that was missing in the source data (20), source data not appropriately recorded (12) or updated retrospectively (12). Further findings identified related to changes to source data that cannot be substantiate (6), source data missing at site (6) and instance where the monitor was not able to verify critical data within source documentation (equal frequency of 6).

It might be argued that the high frequency of source data audit findings relates to short medical notes written by Psychiatrists and medical doctors specifically within the therapeutic area. In a majority of instances the participants symptoms, emotions, activity level and sleep disorders are completed directly onto evaluation checklist and rating scales such as Likert Pain Scale, Patient's Global Impression of Change in Pain (PGIC), SF-36 Health Survey Quality of Life Questionnaire, Work Productivity and Activity Impairment (WPAI) Questionnaire. These become the only source data available. Consequently, data captured in the CRF, eligibility criteria and protocol compliance could not always be confirmed. This resulted in audit findings such as missing information, inappropriate recording of source data; or difficulty to verify critical data within source documentation.

[#] All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Inter-individual rating differences occur in instances when different Investigators (psychiatrist) assess a trial subject. Thus, related to changes to source data that cannot be confirmed. Differences between raters can critically influence study outcomes and should therefore be eliminated before the commencement of the study conduct.

Capturing of insufficient source data could also be a result of poor monitoring (which represents the sixth category with most audit findings (37 audit findings)), ignorance from study team, lack of investigator involvement and insufficient training.

Prior to a clinical trial study planners should clarify and explain in a monitoring manual the expected source data that is required from medical notes. This might ensure that accurate data is derived from medical notes and reported in Case Records Forms.
The monitor should discuss and highlight as early as the initiation visit, the type of information expected to be recorded in the source documents. The monitor should take into account the investigator's procedure of documenting medical procedures and clarify what type of information is routinely recorded at this visit. This could result in pre-identifying medical notes of inferior quality immediately. The monitor could then explain what additional information is required in order to complete the Case Report Form and adhere to protocol requirements. Instances when investigator insists on direct data entry into the CRF a site specific standard operating procedure should be compiled and submitted for approval to clinical management team. If approved it should be provided to auditors during an audit to prevent unsubstantiated findings. Essential source data entries as defined by local regulatory should however be enforced.

4.2.2 Investigational Product (IP)

The second most audit findings (64) 12,65% were derived from deficiencies identified in this audit category relating to *IP*. The majority of findings were no/inadequate documentation of IP receipt at site and IP Inventory Record not maintained up to date (equal frequency of 11). The second most audit findings related to no/inadequate documentation of IP dispensing to patients and IP dosing regime not followed (equal frequency of 8). The latter resulting in protocol violations, which reflected eight audit findings relating to non-compliance with the dosing schedule.

Further findings related to inadequate IP storage facilities for (4). Discrepancies in data between IP accountability log and other study documentation such as CRF (3).

New legislation regarding the dispensing of medication became effective during 2003. Investigators are not allowed to compound or dispense medicine unless he or she is the holder of a license as contemplated in subsection (1) (a) and (section 22 C) of Medicines and Related Substances Act, 1965 (Act No. 101 Of 1965) as amended[16] and Regulations made in terms of the Act (Section 18)[10].
Since 2004/2005 investigators are obligate to obtain an additional dispensing license if IP should be dispense form practice or sub-contract this function to a register pharmacy. Thus, greater attention will be given, at various sites, to maintain accurate records of IP receipt, handling, dispensing and retrieval.

Study planners and monitors should put quality control procedures in place to ensure Investigational Product compliance. This must be implemented from study initiation. An investigational site that does not comply with regulation should not be considered.
Continuous education by study team during site initiation and thereafter should be implemented to ensure accurate IP storage, access control and dispensing.

4.2.3 Study Documentation

Findings in the audit category of *study documentation* were third most prevalent. Fourteen of the audit findings related to inadequate control of study documentation. Other findings in the category related to; translations of key documents, e.g. unavailability of regulatory approval, ethics approval, local language consents forms (8) in the TMF and/or ISF. Six findings related to incomplete study documentation. Delegation of significant trial-related activities not documented (5). Key regulatory submission and approvals were difficult to find. The master patient log did not contain adequate details for identifying the patients (3), and the screening log was not available at the site or had not been completed (3).

These findings could once again be the result of poor monitoring. Monitor's lack of knowledge and experience regarding study documentation requirements and company's standard operating procedures (SOPs) should be considered. Line manager and study planners should ensure that the study team has proper knowledge and understanding of

SOPs requirements. Proper training should address these concerns. This might lead to better understanding of requirements and accurate implementation of the SOPs. Not only should study documentation be identified from study start, but content requirements should be verified and emphasized.

4.2.4 Consent

The audit category reflected fourth most prevalent frequency (46 (9.09%)). Consent findings identified in the category could adversely impact the study's ethical and regulatory integrity and the integrity of patients' participations. This in effect could invalidate the acceptability of patient data or study data in whole.

Consent process not completed prior to study procedures commencing (13) occurred most frequently in this category. This finding was a major for the following indications: Generalized Anxiety Disorder (2), Major Depressive Disorder (1), Migraine (1), Multiple Sclerosis (1), Panic Disorder (1), Post Herpgic Neuralgia Disorder (2), Social Phobia (2), Traumatic Brain Injury (1). It was rated as critical for Migraine.

The second most frequent findings related to patients that had not received copies of the Patient Informed Consent (7). Other significant findings in this audit category included inappropriate consent process procedures (5), informed consent not dated by the subjects (5). The incorrect version of the informed consent used (3) or no signed informed consent available for subjects (3).

Not only is the consent process vital to any clinical study, but emphasis should be placed on the consent process in this particular research field.

To be able to improve the quality of a patients life and to ensure patient safety are crucial aspects of clinical trials. Monitoring of investigational product management should be performed with be monitored. Study planners should ensure that investigators are well-conversant with the consent process. Monitors should know that the review and continuous review of participant consent forms are one of the first monitoring functions to be performed at any investigational site.

As required by ICH GCP[6], SA GCP[8,] 21 CFR part 51[9] and OHRP –Office of Human Research Protection[17] the informed consent clearly state that the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access[*] to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

Thus, if no consent is present or consent process was questionable we cannot access patient's source data or use data.

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[*] **Direct Access**

Permission to examine, analyzes, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

CHAPTER 5

5.0 RECOMMENDATION AND CONCLUSIONS

5.1 Recommendation

The results of this investigation suggested a need for substantial improvement in three important areas. Firstly adherence to the study requirements inclusive of relevant Standard Operating Procedures (SOPs). Secondly the development of better defined protocols and thirdly training of monitors.

It is vital that the importance of protocol adherence is made clear. Site staff should be aware of the implications of protocol deviations. Monitors should be trained to be vigilant. Areas of inadequacy identified during monitoring should be highlighted without delay during a site visit.

Study planners can play a proactive role to reduce the audit findings. Site staff should be educated regarding study conduct expectations. Monitors with experience in this research field should be involved in the study.

The key to a successful trial is the protocol. The protocol should be well written. It is imperative that this is not adapted from the equivalent adult trial and should be written or reviewed by personnel with experience of trials within the specific indication.

Specific attention should be given to the indication under investigation, source data requirements, the informed consent process, study documentation and the procedure regarding IP management.

It is recommended that these results be taken into consideration. Non-compliance with SOPs and regulations are costly to the sponsor and CRO, serving only to delay the drug development process. This is an outcome that is detrimental to both the patient and industry at large.

The small sample may not be representative of the wider picture- however the results are somewhat alarming.

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Alzheimer's Disease			
Major	1	Ethics Committee	SAEs and annual reports were not provided to the ethics committee
Major	2	Source Data	Source data missing at site.
Total	**3**		
Bipolar Disorder			
Major	1	Ethics Committee	No documentary evidence that protocol amendment(s), or revised ICF, was submitted/notified to the EC
Major	1	Facilities	Inadequate Fire Protection where the study is conducted
Major	1	Investigational Product	Certificates of Analysis not available for all batches of medication used.
Major	1	Laboratory/Biological Samples	Inadequate quality control procedures.
Major	1	Protocol and Amendments	Superseded version of the protocol in use at the site
Major	1	Safety Reporting	No evidence of SAE being reported appropriately
Major	1	Source Data	Concerns with the reliability of the source data
Major	1	Study Documentation	Study documentation not adequately controlled
Total	**8**		
Cervical Dystonia			
Major	1	Ethics Committee	No EC approval for the satellite site.
Major	2	Ethics Committee	SAEs and annual reports were not provided to the ethics committee
Major	1	Monitoring	No initiation visit reports on site.
Major	1	Monitoring	Non-compliance with monitoring SOPs
Major	1	Study Documentation	Master patient log did not contain adequate details to identify the patients
Total	**6**		

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Epilepsy			
Major	1	Codebreak Envelopes	Inadequate tracking/confirmation of receipt
Major	2	Consent	Consent and Information Sheet do not contain adequate information
Critical	1	Consent	Consent process not conducted appropriately
Major	1	Investigational Product	Certificates of Analysis not available for all batches of medication used.
Critical	1	Investigational Product	Discrepancies in data between IP accountability log and other study documentation e.g. CRF
Major	2	Investigational Product	No/inadequate documentation of receipt at site
Major	3	Investigator Responsibilities	Inadequate control of the study by the Principal Investigator.
Major	1	Laboratory/Biological Samples	Laboratory samples not handled as detailed in the protocol
Major	1	Monitoring	Inadequate follow up of an issue
Major	1	Monitoring Management	Deficiencies in strategy/documentation of accompanied visits
Critical	2	Protocol and Amendments	Study procedure(s) not described in the protocol
Major	1	Protocol Violations	Multiple protocol violations.
Critical	1	Safety Reporting	Adverse events not reported on the CRF.
Major	2	Safety Reporting	No evidence of SAE being reported appropriately
Major	1	Source Data	Inconsistencies between CRFs and source
Major	1	Study Documentation	No translations of key documents e.g. regulatory and ethics approvals, local language consent forms etc. available.
Major	1	Training	Inadequate strategy for training new staff
Total	**23**		

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Generalised Anxiety Disorder			
Major	1	Codebreak Envelopes	Accidental discarding of the disclosure
Major	2	Consent	Consent process not completed prior to study procedures commencing
Major	1	Consent	Copy of consent form not provided to subject
Major	1	Consent	Incorrect version of the consent form in use
Major	1	Consent	Informed consent not dated by the patient.
Major	1	Consent	No signed consent form available
Major	1	Consent	Patients not signed new information made available during the trial
Major	1	Contract	Non-compliance with contractual obligations
Major	2	CRF Completion	CRF not completed correctly
Major	1	Facilities	Inadequate space to conduct the study
Major	1	Investigational Product	Inadequate storage facilities for IP
Major	2	Investigational Product	IP Inventory Record not maintained up to date
Major	2	Investigational Product	No/inadequate documentation of dispensing to patients
Major	1	Investigational Product	No/inadequate documentation of receipt at site
Major	1	Investigational Product	Re-labelling process deficient
Major	2	Investigator Responsibilities	Inadequate control of the study by the Principal Investigator
Major	1	Monitoring	Backlog in the monitoring and collection of CRFs
Major	2	Monitoring	Inadequate follow up of an issue
Major	1	Monitoring	Monitor not reviewing all source documentation available
Major	1	Monitoring	Protocol violations had not been detected by the monitor.
Major	1	Procedures and Work Instructions	Inadequate control/distribution of project instructions and/or customer SOPs

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Generalised Anxiety Disorder cont.			
Major	1	Protocol and Amendments	Inadequate document control
Major	1	Protocol Violations	Multiple protocol violations.
Major	1	Protocol Violations	Patient not withdrawn despite meeting criteria for withdrawal
Major	1	Source Data	Concerns with the reliability of the source data
Major	1	Source Data	Contradictory information in the source documents
Major	2	Source Data	Inadequate documentation to support patient eligibility
Major	1	Source Data	Information missing in the source data
Major	2	Source Data	Source data missing at site.
Major	1	Source Data	Source data not appropriately recorded
Major	1	Source Data	Source data/patient notes updated retrospectively.
Major	1	Training	Key staff at site not trained in protocol requirements
Major	1	Unassigned	Unassigned
Total	**41**		
Major Depressive Disorder			
Major	1	Clinical Management Plan	Unapproved/incomplete approval
Major	1	Codebreak Envelopes	Inadequate tracking/confirmation of receipt
Major	1	Confidentiality	Client Confidentiality comprised
Major	3	Consent	Consent and Information Sheet do not contain adequate information
Major	2	Consent	Copy of consent form not provided to subject
Major	1	Consent	Incorrect version of the consent form in use
Major	1	Consent	No signed consent form available

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Major Depressive Disorder cont.			
Major	1	Contract	Missing or inadequate documentation of out-of-scope work
Major	1	Contract	Non-compliance with contractual obligation
Major	1	CRF Completion	CRF not completed correctly
Major	3	CRF Completion	CRFs signed prior to completion of CRF
Major	3	Ethics Committee	Documentation submitted to the ethics committee were not available/incomplete
Major	1	Ethics Committee	EC membership list not available or voting members not listed
Major	1	Ethics Committee	EC not compliant with ICH GCP in terms of membership and/or procedure.
Major	1	Ethics Committee	Lack of original ethics committee approval documentation
Major	3	Ethics Committee	No documentary evidence that protocol amendment(s), or revised Informed Consent Form, was submitted/notified to the ethics committee
Major	1	Ethics Committee	Submission documents inaccurate/incomplete
Major	1	Investigational Product	Discrepancies in data between IP accountability log and other study documentation e.g. CRF.
Major	1	Investigational Product	Dosing regime not followed
Major	2	Investigational Product	Inadequate storage facilities for IP
Critical	1	Investigational Product	No record of temperature monitoring of IP storage facility.
Major	1	Investigational Product	No/inadequate documentation of dispensing to patients
Major	1	Investigational Product	No/inadequate documentation of receipt at site
Major	2	Investigator Responsibilities	Inadequate documentation of the delegation of responsibilities to site staff.
Major	1	Investigator Responsibilities	Inappropriate delegation of tasks to inexperienced site staff.

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Major Depressive Disorder cont.			
Major	2	Investigator Responsibilities	Site staff were inadequately qualified and/or supervised.
Major	1	Laboratory/Biological Samples	Inadequate quality control procedures.
Major	1	Laboratory/Biological Samples	Laboratory Accreditation had expired.
Major	3	Laboratory/Biological Samples	No alarm on freezer in case of failure.
Critical	1	Laboratory/Biological Samples	Reference Ranges inadequate/incomplete
Major	1	Monitoring	Follow-up letters not being sent to the site despite problems having been identified.
Critical	2	Monitoring	Inadequate contact with Principal Investigator
Major	1	Monitoring	Monitor unfamiliar with protocol
Major	5	Monitoring	Monitoring visits not conducted according to contractual requirements.
Critical	1	Monitoring	Monitoring Visits not conducted according to contractual requirements.
Major	5	Monitoring Management	Inadequate support of an inexperienced monitor, leading to poor performance.
Major	1	Procedures and Work Instructions	Non compliance with company policy, procedure, work instruction or project instruction
Critical	1	Procedures and Work Instructions	Project Instructions not consistent with contract.
Major	1	Protocol and Amendments	Inadequate handling of protocol amendments
Major	1	Protocol and Amendments	Protocol, or relevant protocol amendments(s), was not on file
Major	1	Protocol Violation	Inadequate communication of protocol violation
Major	2	Protocol Violations	Multiple protocol violations.
Major	1	Protocol Violations	Multiple tests/assessments for one or more patients were not performed
Major	1	Quality Assurance	Audit follow-up inadequate

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Major Depressive Disorder cont.			
Major	1	Records Management	Many documents have inadequate identification or document control features.
Major	1	Regulatory	Relevant regulatory approval documentation not on file
Major	1	Safety Reporting	Documentation of SAE inadequate
Major	1	Safety Reporting	No evidence of SAE being reported appropriately
Major	2	Safety Reporting	SAEs not reported within an appropriate timeframe.
Major	2	Source Data	Changes to source data not recorded appropriately
Major	1	Source Data	Concerns with the reliability of the source data
Major	2	Source Data	Inadequate documentation to support patient eligibility
Critical	1	Source Data	Information missing in the source data
Major	3	Source Data	Information missing in the source data
Major	1	Source Data	Lack of control on source data received from third parties
Major	5	Source Data	Unable to verify critical data within source documentation
Major	5	Study Documentation	Delegation of responsibilities list did not include all trial related activities.
Major	1	Study Documentation	Key regulatory documents e.g. submissions and approvals not easy to locate.
Major	3	Study Documentation	No translations of key documents e.g. regulatory and EC approvals, local language consent forms etc. available.
Major	2	Study Documentation	Screening log not available
Major	1	Study Documentation	Study documentation incomplete
Critical	1	Study Documentation	Study files poorly organized
Major	1	Training	Staff training records incomplete
Total	**103**		

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Migraine			
Critical	1	Consent	Consent process not completed prior to study procedures commencing
Major	2	Contract	Letter of Intent has expired
Major	1	Contract	Missing or inadequate documentation of out-of-scope work
Critical	2	Ethics Committee	SAEs and annual reports were not provided to the ethics committee
Major	1	Investigational Product	No/inadequate documentation of receipt at site
Critical	1	Monitoring	Monitoring visits not conducted according to contractual requirements.
Major	1	Monitoring	Site selection deficiencies
Major	1	Procedures and Work Instructions	Appropriate procedures, work instructions or project instructions are not in place
Major	2	Protocol Violations	Multiple tests/assessments for one or more patients were not performed
Major	2	Protocol Violations	Patient not withdrawn despite meeting criteria for withdrawal
Major	1	Protocol Violations	Tests relevant to the inclusion/exclusion criteria not being reviewed prior to randomization
Major	2	Records Management	Many documents have inadequate identification or document control features
Major	1	Source Data	Information missing in the source data
Major	1	Source Data	Source data not appropriately recorded
Major	2	Study Documentation	Master patient log did not contain adequate details to identify the patients
Major	1	Training	Staff training records incomplete
Total	**22**		

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Multiple Sclerosis			
Major	1	Consent	Consent process not completed prior to study procedures commencing
Major	1	Consent	Copy of consent form not provided to subject
Major	1	Consent	Incorrect version of the consent form in use
Major	1	Consent	Informed consent not dated by the patient.
Major	1	Consent	Patients not signed new information made available during the trial
Major	1	CRF Completion	CRF not completed correctly
Major	1	Investigational Product	Import documentation was not available.
Critical	1	Investigational Product	IP incorrectly prepared for administration.
Major	1	Investigational Product	No record of temperature monitoring of IP storage facility.
Major	2	Investigational Product	No/inadequate documentation of receipt at site
Major	1	Investigational Product	No/inadequate documentation of receipt at site
Major	1	Investigator Responsibilities	Investigator involved in multiple aspects of the study, potential conflict of interest in the roles
Major	1	Monitoring	Monitor not reviewing all source documentation available.
Major	1	Monitoring	Monitoring visit reports/SDV records do not clearly identify the source documentation available
Major	1	Monitoring Management	Inadequate handover or inadequate documentation of the handover of investigator responsibilities at sites
Major	1	Records Management	Archive Strategy not defined or inadequate
Major	1	Regulatory	Discrepancies in the dates of submissions and approvals
Major	1	Regulatory	FDA 1572 out of date.
Major	2	Safety Reporting	Multiple discrepancies between master log of safety reports and the reports either in-house or on site

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Multiple Sclerosis			
Major	2	Safety Reporting	SAEs not reported within an appropriate timeframe
Critical	1	Source Data	Source data not appropriately recorded
Major	1	Source Data	Source data not appropriately recorded
Major	1	Study Documentation	Key regulatory documents e.g. submissions & approvals not easy to locate.
Major	2	Study Documentation	No translations of key documents e.g. regulatory and ethics approvals, local language consent forms etc. available
Major	1	Study Documentation	Screening log not available/completed.
Major	1	Study Documentation	Study documentation not adequately controlled
Major	1	Study Documentation	Study files generally poorly organized
Total	**31**		
Panic Disorder			
Major	1	Consent	Consent process not completed prior to study procedures commencing
Major	1	CRF Completion	Final version of CRF does not comply with the protocol
Major	1	Ethics Committee	EC approval documents do not contain adequate detail
Major	1	Investigational Product	Inadequate/no instructions for IP accountability and reconciliation
Major	3	Investigational Product	IP Inventory Record not maintained up to date
Major	1	Investigational Product	No/inadequate documentation of dispensing to patients
Major	1	Investigational Product	No/inadequate documentation of receipt at site
Major	1	Investigator Responsibilities	Inadequate control of the study by the Principal Investigator
Major	1	Investigator Responsibilities	Inappropriate delegation of tasks to inexperienced site staff.
Major	1	Investigator Responsibilities	Lack of resource to perform study appropriately

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Panic Disorder			
Major	1	Monitoring	Follow-up letters not being sent to the site despite problems having been identified
Major	1	Monitoring	Monitor not reviewing all source documentation available.
Major	1	Safety Reporting	Documentation of SAE inadequate
Major	2	Safety Reporting	SAEs not reported within an appropriate timeframe.
Major	3	Source Data	Changes to source data cannot be substantiated
Major	4	Source Data	Information missing in the source data
Major	5	Source Data	Source data/patient notes updated retrospectively.
Major	4	Study Documentation	Study documentation incomplete
Total	**33**		
Parkinson's			
Major	1	Codebreak Envelopes	Codebreak envelopes opened without adequate written explanation
Major	2	Ethics Committee	EC approval documents do not contain adequate detail
Major	1	Investigational Product	IP expired
Major	1	Investigator Responsibilities	Inadequate documentation of the delegation of responsibilities to site staff.
Major	1	Laboratory/Biological Samples	Laboratory report(s) missing.
Major	1	Monitoring Management	Inadequate support of an inexperienced monitor,
Major	1	Source Data	Source data missing at site.
Major	1	Study Documentation	No translations of key documents e.g. regulatory and ethics approvals, local language consent forms etc. available.
Major	1	Study Documentation	Study documentation not adequately controlled
Total	**10**		

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Post Herpgic Neuralgia			
Major	1	Analysis	Unexplained change in analysis.
Major	1	Clinical Management Plan	Unapproved/incomplete approval
Major	2	Consent	Consent process not completed prior to study procedures commencing
Major	1	Contract	Non-compliance with contractual obligations
Major	1	CRF Completion	CRF inconsistent with source documents
Major	1	Ethics Committee	Written ethics committee approval for original protocol or significant protocol amendment was not on file
Major	1	Investigational Product	No/inadequate documentation of dispensing to patients
Major	1	Laboratory/Biological Samples	Reference ranges inadequate/incomplete
Major	1	Procedures and Work Instructions	Procedures required by regulations are not in place
Total	**10**		
Schizophrenia			
Major	1	Clinical Management Plan	Key sections missing
Major	1	Clinical Management Plan	Unapproved/incomplete approval
Major	1	Codebreak Envelopes	Accidental discarding of code break at site
Major	1	Consent	Consent and Information Sheet do not contain adequate information
Major	1	Consent	Informed consent not dated by the patient.
Critical	1	Consent	Questionable patient signatures of consent
Major	1	Ethics Committee	Documents submitted to the ethics committee were not available/incomplete
Critical	1	Ethics Committee	No EC approval for the satellite site.
Major	1	Ethics Committee	Written ethics committee approval for original protocol or significant protocol amendment was not on file

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Schizophrenia			
Critical	1	Investigational Product	Discrepancies in data between IP accountability log and other study documentation e.g. CRF.
Major	1	Investigational Product	Dosing regime not followed
Major	1	Investigational Product	Inadequate storage facilities for IP
Major	1	Investigational Product	Incorrect IP dispensed to patients
Critical	1	Investigational Product	Label did not meet requirements of Annex 13/local regulatory requirements
Critical	2	Investigational Product	No/inadequate documentation of dispensing to patients
Major	1	Investigational Product	Re-labelling process deficient
Critical	1	Investigator Responsibilities	Poor understanding by site staff of the protocol requirements
Major	1	Investigator Responsibilities	Inadequate control of the study by the Principal Investigator.
Major	1	Investigator Responsibilities	Inadequate documentation of the delegation of responsibilities to site staff.
Critical	1	Investigator Responsibilities	Site staff were inadequately qualified and/or supervised
Major	2	Investigator Responsibilities	Site staff were inadequately qualified and/or supervised
Major	1	Monitoring	Monitoring visits not conducted according to contractual requirements.
Major	1	Monitoring	Protocol violations had not been detected by the monitor
Critical	1	Monitoring	Site selection deficiencies
Major	1	Monitoring	Visit reports were not issued within the required timelines
Major	1	Monitoring Management	Inadequate support of an inexperienced monitor, leading to poor performance.
Major	1	Procedures and Work Instructions	Non compliance with company policy, procedure, work instruction or project instruction

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Schizophrenia			
Major	1	Protocol and Amendments	Inadequate handling of protocol amendments
Major	1	Protocol Violations	Inadequate communication of protocol violations
Major	1	Protocol Violations	Multiple protocol violations.
Major	1	Protocol Violations	Non-compliance with the dose schedule.
Major	1	Protocol Violations	Safety data not assessed prior to administration of study drug
Critical	1	Quality Management	Inadequate management of quality issues
Major	1	Regulatory	Relevant regulatory approval/notification documentation not on file at the site
Major	1	Resources	Inadequate/inappropriate resource allocated
Major	1	Safety Reporting	No evidence of SAE being reported appropriately
Major	1	Safety Reporting	SAEs not reported within an appropriate timeframe.
Critical	1	Source Data	Contradictory information in the source documents
Major	1	Source Data	False or fabricated data entered.
Critical	1	Source Data	Inadequate documentation to support patient eligibility
Major	1	Source Data	Information missing in the source data
Critical	1	Source Data	Significant inconsistencies between CRF and source document
Major	1	Study Documentation	Key regulatory documents e.g. submissions & approvals not easy to locate.
Major	1	Study Documentation	Study documentation incomplete
Major	1	Study Documentation	Study documentation not adequately controlled
Major	1	Study Documentation	Study files generally poorly organized
Major	1	Training	Project specific training inadequate

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Schizophrenia			
Major	1	Training	Training strategy not documented or inadequately documented
Total	**50**		
Social Phobia			
Major	4	Consent	Consent process not completed prior to study procedures commencing
Major	1	Consent	Consent process not conducted appropriately
Major	3	Consent	Copy of consent form not provided to subject
Major	1	Consent	Inadequate version control
Major	2	Consent	Informed consent not dated by the patient.
Major	1	Contract	No finalised contract/scope of work available for the study.
Major	1	CRF Completion	CRF inconsistent with source documents
Major	1	CRF Completion	No CRF completed for screen failure subject
Major	1	Essential Documents	No insurance certificate available
Major	1	Ethics Committee	Documents submitted to the ethics committee were not available/incomplete
Major	1	Ethics Committee	Lack of original ethics committee approval documentation
Major	2	Ethics Committee	Protocol amendment implemented prior to EC approval
Major	4	Investigational Product	Dosing regime not followed
Major	1	Investigational Product	Inadequate/no documentation of return of IP to patients
Major	5	Investigational Product	IP Inventory Record not maintained up to date
Major	1	Investigational Product	Label did not meet requirements of Annex 13/local regulatory requirements
Major	1	Investigational Product	Monitor completed the IP Inventory Record.

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Social Phobia cont			
Major	1	Investigational Product	No/inadequate documentation of dispensing to patients
Major	2	Investigational Product	No/inadequate documentation of receipt at site
Major	1	Investigational Product	No/inadequate documentation of retrieval from site
Major	2	Investigational Product	Potential unblinding of study personnel
Major	3	Investigator Responsibilities	Inadequate control of the study by the Principal Investigator
Major	2	Laboratory/Biological Samples	Laboratory samples not handled as detailed in the protocol
Major	4	Laboratory/Biological Samples	Slow reporting of laboratory results
Critical	1	Monitoring	Inadequate follow up of an issue
Major	3	Monitoring	Inadequate follow up of an issue
Major	2	Monitoring	Monitor unfamiliar with protocol
Major	1	Monitoring	Non-compliance with monitoring SOPs
Major	1	Monitoring	Site selection deficiencies
Major	1	Monitoring Management	Deficiencies in strategy/documentation of accompanied visits
Major	1	Monitoring Management	Inadequate support of an inexperienced monitor, leading to poor performance
Major	1	Monitoring Management	Visit reports on file not signed by monitor and/or CTL
Major	1	Procedures and Work Instructions	Non compliance with company policy, procedure, work instruction or project instructions
Major	1	Protocol and Amendments	Amendment implemented prior to approval
Major	2	Protocol and Amendments	Inadequate document control
Major	2	Protocol Violations	Documentation of protocol violations/deviations not adequate.
Major	6	Protocol Violations	Multiple protocol violations.

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Social Phobia cont.			
Major	2	Protocol Violations	Multiple tests/assessments for one or more patients were not performed
Major	6	Protocol Violations	Non-compliance with the dose schedule.
Major	2	Protocol Violations	Patient not withdrawn despite meeting criteria for withdrawal
Major	2	Protocol Violations	Patient visits not conducted within the time period laid out in the protocol
Major	1	Protocol Violations	Safety data not assessed prior to administration of study drug
Major	3	Protocol Violations	Tests relevant to the inclusion/exclusion criteria not being reviewed prior to randomization
Major	1	Records Management	Many documents have inadequate identification or document control features.
Major	2	Recruitment and Randomisation	Multiple issues regarding recruitment of patients
Major	1	Safety Reporting	Handling of safety updates/IND alert letters inadequate
Major	1	Safety Reporting	No evidence of SAE being reported appropriately
Major	1	Source Data	Computer print-outs not signed and dated
Major	4	Source Data	Concerns with the reliability of the source data
Major	1	Source Data	Inadequate documentation to support patient eligibility
Major	8	Source Data	Information missing in the source data
Major	1	Source Data	Lack of control on source data received from third parties
Major	2	Source Data	Source data missing at site.
Critical	1	Source Data	Source data not appropriately recorded
Major	6	Source Data	Source data not appropriately recorded
Major	6	Source Data	Source data/patient notes updated retrospectively.
Major	1	Source Data	Unable to verify critical data within source documentation.

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Social Phobia cont.			
Major	1	Study Documentation	Correction fluid used on study
Major	1	Study Documentation	No translations of key documents e.g. regulatory and ethics approvals, local language consent forms etc. available
Major	1	Study Documentation	Study documentation incomplete
Major	8	Study Documentation	Study documentation not adequately controlled
Major	1	Study Documentation	Study documentation not finalised at the appropriate time
Total	**133**		
Spasticity			
Major	1	Investigational Product	IP Inventory Record not maintained up to date
Major	1	Protocol Violations	Non-compliance with the dose schedule.
Major	1	Source Data	Inadequate documentation to support patient eligibility
Total	**3**		
Traumatic Brain Injury			
Major	1	Consent	Consent process not completed prior to study procedures commencing
Major	1	Consent	Consent process not conducted appropriately
Major	1	Consent	Consent process not conducted appropriately
Major	1	Consent	Consent process not conducted appropriately
Major	1	Consent	Inadequate version control
Critical	1	Consent	No signed consent form available
Major	1	Contract	Contract between Quintiles and Investigator not available
Major	1	CRF Completion	CRF not completed correctly

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Traumatic Brain Injury cont.			
Major	1	CSV	CSV documentation does not meet regulatory requirements
Major	1	Investigational Product	Dosing regime not followed
Major	1	Investigational Product	Dosing regime not followed
Major	1	Investigational Product	Inadequate/no documentation of return of IP from patient
Major	1	Laboratory/Biological Samples	Inadequate follow-up and documentation of out-of-range values.
Major	1	Laboratory/Biological Samples	Inadequate follow-up and documentation of out-of-range values
Major	1	Laboratory/Biological Samples	Inadequate follow-up and documentation of out-of-range values
Major	1	Laboratory/Biological Samples	Inadequate follow-up and documentation of out-of-range values.
Major	1	Monitoring	Monitor not reviewing all source documentation available.
Major	1	Records Management	Many documents have inadequate identification or document control features
Major	1	Recruitment and Randomisation	Multiple issues regarding recruitment of patients
Major	1	Safety Reporting	Inadequate follow-up of SAE(s)
Major	1	Safety Reporting	Inadequate follow-up of SAE(s)
Major	1	Safety Reporting	SAEs not reported within an appropriate timeframe
Major	1	Safety Reporting	SAEs not reported within an appropriate timeframe
Major	1	Safety Reporting	SAEs not reported within an appropriate timeframe.
Major	1	Source Data	Changes to source data not recorded appropriately
Major	1	Source Data	Information missing in the source data
Major	1	Source Data	Source data not appropriately recorded
Major	1	Study Documentation	Study documentation not adequately controlled

APPENDIX A: AUDIT FINDING ANALYSIS PER INDICATION

Severity	Frequency	Category	Finding
Traumatic Brain Injury cont			
Major	1	Study Documentation	Study documentation not adequately controlled
Major	1	Training	Project specific training inadequate
Total	**30**		

APPENDIX B: RE-OCCURING AUDIT FINDINGS PER CATEGORY

Severity	Frequency	Category	Finding
		Analysis	
Major	1	Analysis	Unexplained change in analysis.
Total	**1**		
		Clinical Management Plan	
Major	1	Clinical Management Plan	Key sections missing
Major	3	Clinical Management Plan	Unapproved/incomplete approval
Total	**4**		
		Codebreak Envelopes	
Major	1	Codebreak Envelopes	Accidental discarding of codebreak at site
Major	1	Codebreak Envelopes	Accidental discarding of the disclosure
Major	1	Codebreak Envelopes	Codebreak envelopes opened without adequate written explanation
Major	2	Codebreak Envelopes	Inadequate tracking/confirmation of receipt
Total	**5**		
		Confidentiality	
Major	1	Confidentiality	Client Confidentiality comprised
Total	**1**		
		Consent	
Major	17	Consent	Consent process not completed prior to study procedure commencing
Critical	1	Consent	Consent process not completed prior to study procedures commencing
Critical	1	Consent	Consent process not conducted appropriately
Major	4	Consent	Consent process not conducted appropriately
Major	7	Consent	Copy of consent form not provided to subject
Major	2	Consent	Inadequate version control

APPENDIX B: RE-OCCURING AUDIT FINDINGS PER CATEGORY

Severity	Frequency	Category	Finding
Major	3	Consent	Incorrect version of the consent form in use
Major	5	Consent	Informed consent not dated by the patient.
Critical	1	Consent	No signed consent form available
Major	2	Consent	No signed consent form available
Major	2	Consent	Patients not signed new information made available during the trial
Critical	1	Consent	Questionable patient signatures of consent
Total	**46**		
		Contract	
Major	1	Contract	Contract between Quintiles and Investigator not available
Major	2	Contract	Letter of Intent has expired
Major	2	Contract	Missing or inadequate documentation of out-of-scope work
Major	1	Contract	No finalised contract/scope of work available for the study.
Major	3	Contract	Non-compliance with contractual obligation
Total	**9**		
		CRF Completion	
Major	2	CRF Completion	CRF inconsistent with source documents
Major	5	CRF Completion	CRF not completed correctly
Major	3	CRF Completion	CRFs signed prior to completion of CRF
Major	1	CRF Completion	Final version of CRF does not comply with the protocol
Major	1	CRF Completion	No CRF completed for screen failure subject
Total	**12**		

APPENDIX B: RE-OCCURING AUDIT FINDINGS PER CATEGORY

Severity	Frequency	Category	Finding
		CSV	
Major	1	CSV	CSV documentation does not meet regulatory requirements
Total	**1**		
		Essential Documents	
Major	1	Essential Documents	No insurance certificate available
Total	**1**		
		Ethics Committee	
Major	5	Ethics Committee	Documents submitted to the ethics committee were not available /incomplete.
Major	3	Ethics Committee	EC approval documents do not contain adequate detail
Major	1	Ethics Committee	EC membership list not available or voting members not listed
Major	1	Ethics Committee	EC not compliant with ICH GCP in terms of membership and/or procedure.
Major	2	Ethics Committee	Lack of original ethics committee approval documentation
Major	4	Ethics Committee	No documentary evidence that protocol amendment(s), or revised Informed Consent Form, was submitted/notified to the ethics committee
Critical	1	Ethics Committee	No EC approval for the satellite site.
Major	1	Ethics Committee	No EC approval for the satellite site.
Major	2	Ethics Committee	Protocol amendment implemented prior to EC approval
Critical	2	Ethics Committee	SAEs and annual reports were not provided to the ethics committee
Major	3	Ethics Committee	SAEs and annual reports were not provided to the ethics committee
Major	1	Ethics Committee	Submission documents inaccurate/incomplete
Major	2	Ethics Committee	Written EC approval for original protocol or protocol amendment not filed
Total	**28**		

APPENDIX B: RE-OCCURING AUDIT FINDINGS PER CATEGORY

Severity	Frequency	Category	Finding
		Facilities	
Major	1	Facilities	Inadequate Fire Protection where the study is conducted
Major	1	Facilities	Inadequate space to conduct the study
Total	**2**		
		Investigational Product	
Major	2	Investigational Product	Certificates of Analysis not available for all batches of medication used.
Critical	2	Investigational Product	Discrepancies in data between IP accountability log and other study documentation e.g. CRF
Major	1	Investigational Product	Discrepancies in data between IP accountability log and other study documentation e.g. CRF.
Major	8	Investigational Product	Dosing regime not followed
Major	1	Investigational Product	Import documentation was not available.
Major	4	Investigational Product	Inadequate storage facilities for IP
Major	2	Investigational Product	Inadequate/no documentation of return of IP from patient
Major	1	Investigational Product	Inadequate/no instructions for IP accountability and reconciliation
Major	1	Investigational Product	Incorrect IP dispensed to patients
Major	1	Investigational Product	IP expired
Critical	1	Investigational Product	IP incorrectly prepared for administration.
Major	11	Investigational Product	IP Inventory Record not maintained up to date
Critical	1	Investigational Product	Label did not meet requirements of Annex 13/local regulatory requirements
Major	1	Investigational Product	Label did not meet requirements of Annex 13/local regulatory requirements
Major	1	Investigational Product	Monitor completed the IP Inventory Record.
Critical	1	Investigational Product	No record of temperature monitoring of IP storage facility.

APPENDIX B: Re-OCCURING AUDIT FINDINGS PER CATEGORY

Severity	Frequency	Category	Finding
Major	1	Investigational Product	No record of temperature monitoring of IP storage facility.
Critical	2	Investigational Product	No/inadequate documentation of dispensing to patients
Major	6	Investigational Product	No/inadequate documentation of dispensing to patients
Major	11	Investigational Product	No/inadequate documentation of receipt at site
Major	1	Investigational Product	No/inadequate documentation of retrieval from site
Major	2	Investigational Product	Potential unblinding of study personnel
Major	2	Investigational Product	Re-labelling process deficient
Total	**64**		
		Investigator Responsibilities	
Major	8	Investigator Responsibilities	Inadequate control of the study by the Principal Investigator.
Major	2	Investigator Responsibilities	Inadequate documentation of the delegation of responsibilities to site staff.
Major	1	Investigator Responsibilities	Inappropriate delegation of tasks to inexperienced site staff.
Critical	1	Investigator Responsibilities	Poor understanding by site staff of the protocol requirements
Major	1	Investigator Responsibilities	Site staff were inadequately qualified and/or supervised.
Major	2	Investigator Responsibilities	Inadequate control of the study by the Principal Investigator
Major	2	Investigator Responsibilities	Inadequate documentation of the delegation of responsibilities to site staff.
Major	1	Investigator Responsibilities	Inappropriate delegation of tasks to inexperienced site staff.
Major	1	Investigator Responsibilities	Investigator involved in multiple aspects of the study, potential conflict of interest in the roles
Major	1	Investigator Responsibilities	Lack of resource to perform study appropriately
Critical	1	Investigator Responsibilities	Site staff were inadequately qualified and/or supervised
Major	3	Investigator Responsibilities	Site staff were inadequately qualified and/or supervised
Total	**24**		

APPENDIX B: Re-OCCURING AUDIT FINDINGS PER CATEGORY

Severity	Frequency	Category	Finding
		Laboratory/Biological Samples	
Major	4	Laboratory/Biological Samples	Inadequate follow-up and documentation of out-of-range values.
Major	2	Laboratory/Biological Samples	Laboratory samples not handled as detailed in the protocol
Major	4	Laboratory/Biological Samples	Slow reporting of laboratory results
Major	2	Laboratory/Biological Samples	Inadequate quality control procedures.
Major	1	Laboratory/Biological Samples	Laboratory Accreditation had expired.
Major	1	Laboratory/Biological Samples	Laboratory report(s) missing.
Major	1	Laboratory/Biological Samples	Laboratory samples not handled as detailed in the protocol
Major	3	Laboratory/Biological Samples	No alarm on freezer in case of failure.
Major	1	Laboratory/Biological Samples	Reference ranges inadequate/incomplete
Critical	1	Laboratory/Biological Samples	Reference ranges inadequate/incomplete
Total	**20**		
		Monitoring	
Major	1	Monitoring	Backlog in the monitoring and collection of CRFs
Major	2	Monitoring	Follow-up letters not being sent to the site despite problems having been identified
Critical	2	Monitoring	Inadequate contact with Principal Investigator
Critical	1	Monitoring	Inadequate follow up of an issue
Major	6	Monitoring	Inadequate follow up of an issue
Major	4	Monitoring	Monitor not reviewing all source documentation available
Major	3	Monitoring	Monitor unfamiliar with protocol
Major	1	Monitoring	Monitoring visit reports/SDV records do not clearly identify the source documentation available

APPENDIX B: Re-OCCURING AUDIT FINDINGS PER CATEGORY

Severity	Frequency	Category	Finding
Critical	2	Monitoring	Monitoring visits not conducted according to contractual requirements.
Major	6	Monitoring	Monitoring visits not conducted according to contractual requirements.
Major	1	Monitoring	No initiation visit reports on site.
Major	2	Monitoring	Non-compliance with monitoring SOPs
Major	2	Monitoring	Protocol violations had not been detected by the monitor
Critical	1	Monitoring	Site selection deficiencies
Major	2	Monitoring	Site selection deficiencies
Major	1	Monitoring	Visit reports were not issued within the required timelines
	37		
		Monitoring Management	
Major	2	Monitoring Management	Deficiencies in strategy/documentation of accompanied visits
Major	1	Monitoring Management	Inadequate handover or inadequate documentation of the handover of investigator responsibilities at sites
Major	8	Monitoring Management	Inadequate support of an inexperienced monitor, leading to poor performance.
Major	1	Monitoring Management	Visit reports on file not signed by monitor and/or CTL
Total	**12**		
		Procedures and Work Instructions	
Major	1	Procedures and Work Instructions	Appropriate procedures, work instructions or project instructions are not in place
Major	1	Procedures and Work Instructions	Inadequate control/distribution of project instructions and/or customer SOPs
Major	3	Procedures and Work Instructions	Non compliance with company policy, SOP, work instruction or project instructions
Major	1	Procedures and Work Instructions	Procedures required by regulations are not in place
Critical	1	Procedures and Work Instructions	Project Instructions not consistent with contract.
Total	**7**		

APPENDIX B: Re-OCCURING AUDIT FINDINGS PER CATEGORY

Severity	Frequency	Category	Finding
		Protocol and Amendments	
Major	1	Protocol and Amendments	Amendment implemented prior to approval
Major	3	Protocol and Amendments	Inadequate document control
Major	2	Protocol and Amendments	Inadequate handling of protocol amendments
Major	1	Protocol and Amendments	Protocol, or amendments(s), not on file
Critical	1	Protocol and Amendments	Study procedure(s) not described in the protocol
Major	1	Protocol and Amendments	Study procedure(s) not described in the protocol
Major	1	Protocol and Amendments	Superseded version of the protocol in use at the site
Total	**10**		
		Protocol Violations	
Major	2	Protocol Violations	Documentation of protocol violations/deviations not adequate.
Major	2	Protocol Violations	Inadequate communication of protocol violations
Major	11	Protocol Violations	Multiple protocol violations.
Major	5	Protocol Violations	Multiple tests/assessments for one or more patients were not performed
Major	8	Protocol Violations	Non-compliance with the dose schedule.
Major	5	Protocol Violations	Patient not withdrawn despite meeting criteria for withdrawal
Major	2	Protocol Violations	Patient visits not conducted within the time period laid out in the protocol
Major	2	Protocol Violations	Safety data not assessed prior to administration of study drug
Major	4	Protocol Violations	Inclusion/exclusion tests not being reviewed prior to randomisation
Total	**41**		
		Quality Assurance	
Major	1	Quality Assurance	Audit follow-up inadequate
Total	**1**		

APPENDIX B: Re-OCCURING AUDIT FINDINGS PER CATEGORY

Severity	Frequency	Category	Finding
		Quality Management	
Critical	1	Quality Management	Inadequate management of quality issues
Total	**1**		
		Records Management	
Major	1	Records Management	Archive Strategy not defined or inadequate
Major	5	Records Management	Many documents have inadequate identification or document control features.
Total	**6**		
		Recruitment and Randomisation	
Major	3	Recruitment and Randomisation	Multiple issues regarding recruitment of patients
Total	**3**		
		Regulatory	
Major	1	Regulatory	Discrepancies in the dates of submissions and approvals
Major	1	Regulatory	FDA 1572 out of date.
Major	2	Regulatory	Relevant regulatory approval documentation not on file
Total	**4**		
		Resources	
Major	1	Resources	Inadequate/inappropriate resource allocated
Total	**1**		
		Safety Reporting	
Critical	1	Safety Reporting	Adverse events not reported on the CRF.
Major	2	Safety Reporting	Documentation of SAE inadequate
Major	1	Safety Reporting	Handling of safety updates/IND alert letters inadequate

APPENDIX B: Re-OCCURING AUDIT FINDINGS PER CATEGORY

Severity	Frequency	Category	Finding
Major	2	Safety Reporting	Inadequate follow-up of SAE(s)
Major	2	Safety Reporting	Multiple discrepancies between master log of safety reports and the reports either in-house or on site
Major	6	Safety Reporting	No evidence of SAE being reported appropriately
Major	10	Safety Reporting	SAEs not reported within the appropriate timeframe.
Total	**24**		
		Source Data	
Major	6	Source Data	Changes to source data not recorded appropriately
Critical	1	Source Data	Contradictory information in the source documents
Major	9	Source Data	Contradictory information in the source documents
Major	1	Source Data	False or fabricated data entered.
Critical	1	Source Data	Inadequate documentation to support patient eligibility
Major	6	Source Data	Inadequate documentation to support patient eligibility
Major	1	Source Data	Inconsistencies between CRFs and source
Critical	1	Source Data	Information missing in the source data
Major	19	Source Data	Information missing in the source data
Major	2	Source Data	Lack of control on source data received from third parties
Critical	1	Source Data	Significant inconsistencies between CRF and source document
Major	7	Source Data	Source data missing at site.
Critical	2	Source Data	Source data not appropriately recorded
Major	10	Source Data	Source data not appropriately recorded
Major	12	Source Data	Source data updated retrospectively.
Major	6	Source Data	Unable to verify critical source data
Total	**85**		

APPENDIX B: Re-OCCURING AUDIT FINDINGS PER CATEGORY

Severity	Frequency	Category	Finding
		Study Documentation	
Major	1	Study Documentation	Correction fluid used on study
Major	5	Study Documentation	Delegation of responsibilities list did not include all significant trial related activities.
Major	3	Study Documentation	Key regulatory documents e.g. submissions and approvals not easy to locate.
Major	3	Study Documentation	Master patient log did not contain adequate details to identify the patients
Major	8	Study Documentation	No translations of key documents e.g. regulatory and ethics approvals, local language consent forms etc. available.
Major	3	Study Documentation	Screening log not available/completed.
Major	7	Study Documentation	Study documentation incomplete
Major	14	Study Documentation	Study documentation not adequately controlled
Major	1	Study Documentation	Study documentation not finalised at the appropriate time
Major	2	Study Documentation	Study files generally poorly organized
Critical	1	Study Documentation	Study files generally poorly organized
Total	**48**		
		Training	
Major	1	Training	Inadequate strategy for training new staff
Major	1	Training	Key staff at site not trained in protocol requirements
Major	2	Training	Project specific training inadequate
Major	2	Training	Staff training records incomplete
Major	1	Training	Training strategy not documented or inadequately documented
Total	**7**		

APPENDIX B: Re-OCCURING AUDIT FINDINGS PER CATEGORY

Severity	Frequency	Category	Finding
		Unassigned	
Major	1	Unassigned	Unassigned
Total	**1**		
Total	**506**		

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Louw

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M040834**
PROJECT	An Assessment of Audit Findings for Clinical Trials Involving Central Nervous Systems (CNS) Studies
INVESTIGATORS	Ms E Louw
DEPARTMENT	School of Therapeutic Sciences
DATE CONSIDERED	04.08.27
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 04.08.30 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr G Lowndes

DECLARATION OF INVESTIGATOR(S)

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

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

REFERENCES

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