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# A frequency trend analysis of major and critical audit finding groupings for clinical trials involving central nervous system studies

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# 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

Pretoria, 2008

## 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

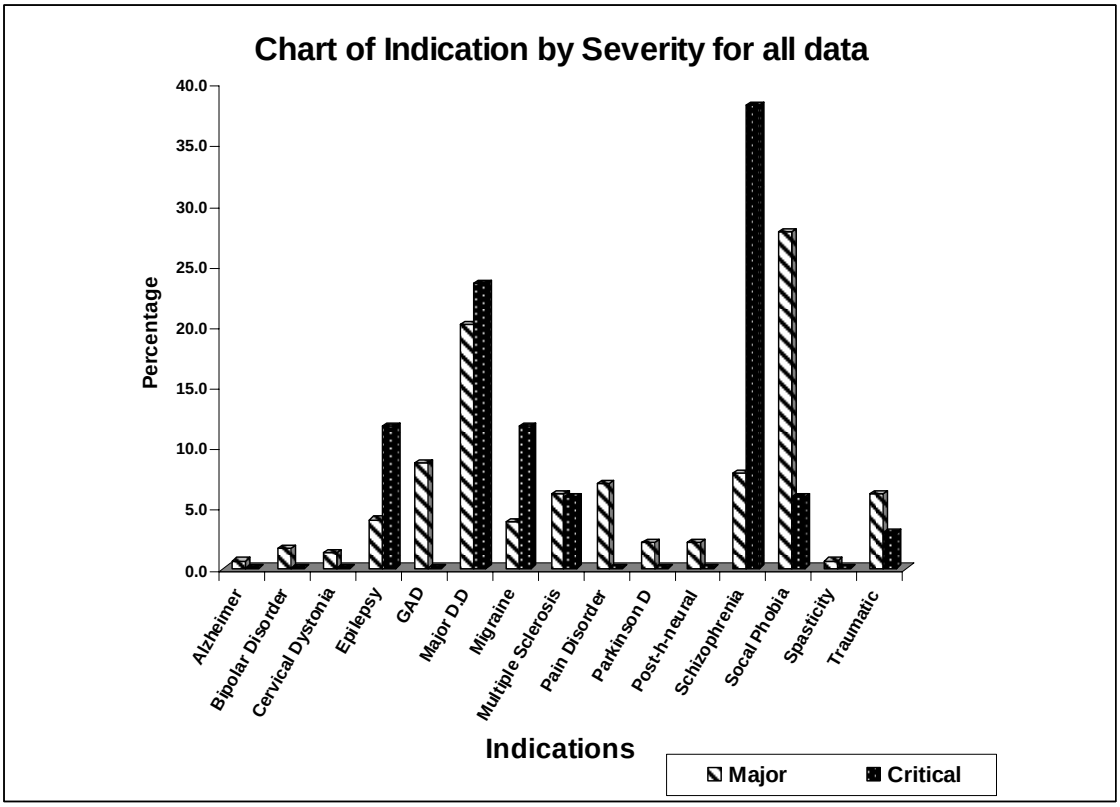



Figure 3.2 and figure 3.3 serve as graphic representations of the percentage audit findings rated as major or critical for each indication per region.

**Figure 3.2** Indications by Severity for Europe

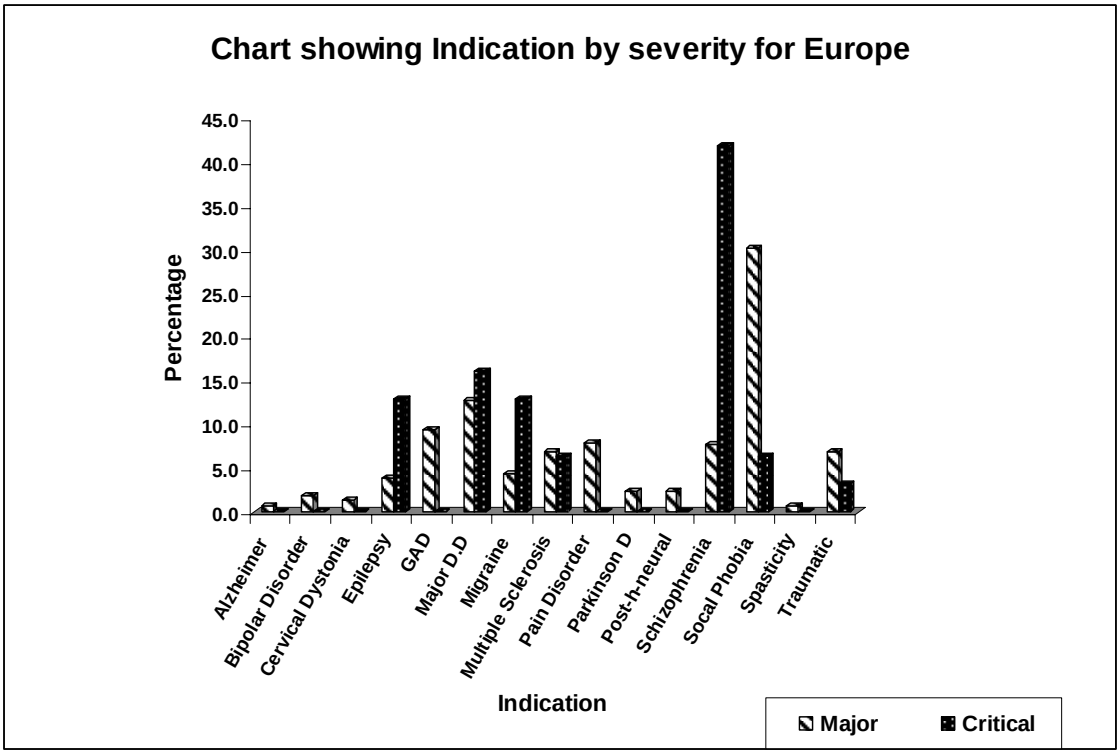
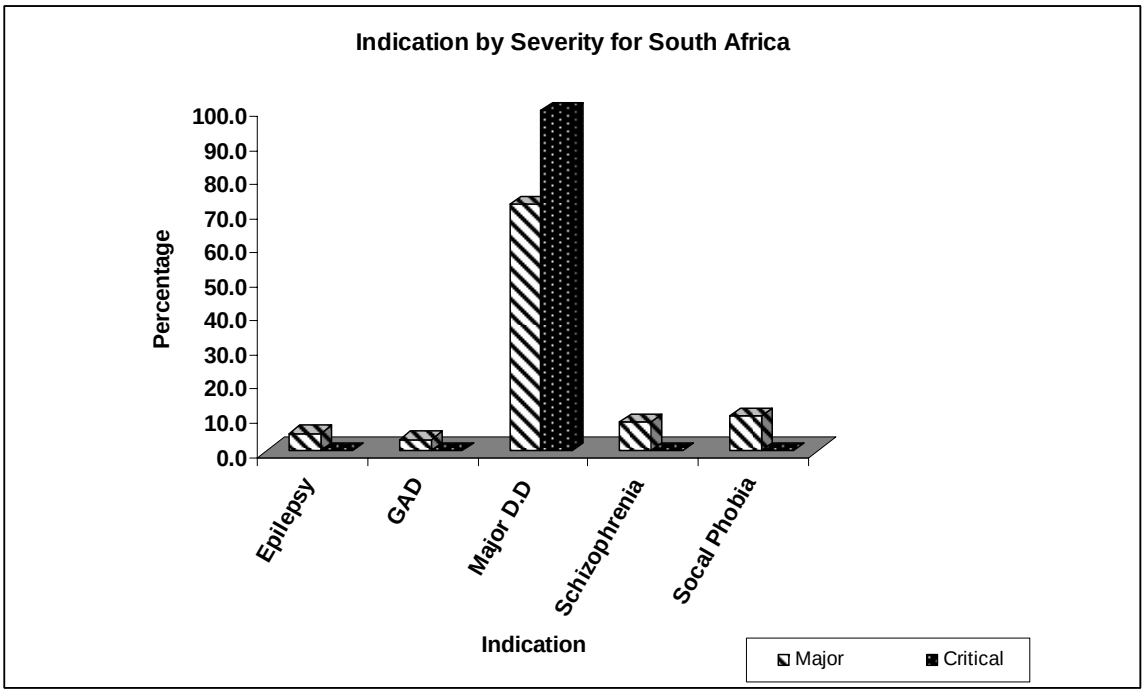



**Figure 3.3** Indications by Severity for South Africa



### 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.

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[#] 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

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**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

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