PROFILE OF CLINICAL TRIAL BIOSTATISTICIANS AND UNIVERSITY COURSES TO TRAIN THEM IN SOUTH AFRICA

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DECLARATION

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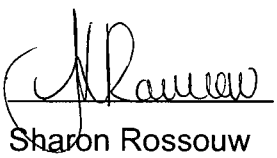

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ABSTRACT

Many statistical issues in the area of clinical trials are specific to this particular field. A clinical trial biostatistician should not only be appropriately qualified in general statistical theory, but also be appropriately trained and experienced in the application of statistics to clinical trials. This thesis investigates the background and training of statisticians practicing in this field in South Africa. It provides an overview of the training that is available for clinical trial biostatisticians at universities in South Africa. Lastly, the thesis also provides recommendations for the training and development of clinical trial biostatisticians.

The methodology used for this research included a literature study regarding the required profile (education/training, years of experience and part of the industry in which they are employed) of a clinical trial biostatistician, and topics of interest to such a biostatistician. A review of the content of statistics courses offered at South African Universities was performed. A questionnaire survey was conducted to assess the education/training profile of clinical trial biostatisticians in South Africa and to assess the knowledge of biostatisticians in areas considered necessary to be an appropriately qualified and experienced clinical trial biostatistician as defined in the literature.

Twenty-nine respondents were considered valid clinical trial biostatisticians and were thus included in the analysis of the clinical trial biostatistician questionnaires. Twenty South African universities were approached to provide information regarding the statistics courses they present. Information was obtained from fourteen (70.0%) of these universities.

The profile of clinical trial biostatisticians in South Africa, with respect to qualifications and experience, is comparable to clinical trial biostatisticians in Europe. However, the industries in which the biostatisticians are employed differ from those that employ clinical trial biostatisticians in Europe.

South African clinical trial biostatisticians are not necessarily familiar with all the topics applicable to their discipline. The areas in which they were the least familiar were: regulatory requirements and international guidelines, statistical analysis considerations, reporting, and quality control and documentation. Aside from statistical methods which were mostly learned at university, knowledge and experience were mostly acquired through on-the-job training followed by self-study and reading.

It is hoped that the implementation of a university programme specific to clinical trial biostatisticians, improvements in current statistical courses, the development of a clinical trial biostatistician manual and the introduction of a medical statistician certification scheme, would contribute to developing what Iman (1995) is referring to when he quotes Kettenring in saying, "Industry needs holistic statisticians who are nimble problem solvers".

Keywords: clinical trial, biostatistician, training, experience, knowledge

ABSTRAK

Baie statistiese kwessies op die gebied van kliniese proewe is van spesifieke toepassing op hierdie veld. 'n Kliniese proef biostatistikus moet nie net toepaslik gekwalifiseer wees rakende algemene statistiese teorie nie, maar moet ook genoegsaam opgelei en ervare wees ten opsigte van die toepassing van statistiek in kliniese proewe. Hierdie verhandeling ondersoek die agtergrond en opleiding van statistici werksaam op hierdie gebied in Suid-Afrika. 'n Oorsig word verskaf van die opleiding wat beskikbaar is vir kliniese proef biostatistici by universiteite in Suid-Afrika. Laastens word aanbevelings gemaak vir die opleiding en ontwikkeling van kliniese proef biostatistici.

Die metodologie wat vir hierdie navorsing gebruik is, het 'n literatuurstudie rakende die vereiste profiel van 'n kliniese proef biostatistikus (opleiding, ondervindingsjare en gedeelte van die bedryf waar hulle in diens is), asook sake wat vir 'n biostatistikus van belang is, ingesluit. 'n Oorsig oor die inhoud van statistiekkursusse wat by Suid-Afrikaanse universiteite aangebied word, word gegee. 'n Vraelysopname is uitgevoer om die opleidingsprofiel van kliniese proef biostatistici in Suid-Afrika te ondersoek. Die vakgebiede wat as noodsaaklik beskou word ten einde na behore gekwalifiseerd en ervare as 'n kliniese proef biostatistikus te wees is in die literatuur geïdentifiseer en die kennis van biostatistici is hiervolgens geëvalueer.

Nege-en-twintig respondente is as geldige kliniese proef biostatistici beskou en is derhalwe ingesluit in die analise van die kliniese proef biostatistikus vraelys. Twintig Suid-Afrikaanse universiteite is genader vir inligting oor die statistiekkursusse wat aangebied word. Inligting is van veertien (70%) van hierdie universiteite ontvang.

Die profiel van kliniese proef biostatistici, met betrekking tot hulle kwalifikasies en ondervinding, is vergelykbaar met dié van kliniese proef biostatistici in Europa, maar die spesifieke deel van die industrie waarin hierdie biostatistici werksaam is, verskil van die wat in Europa werk.

Suid-Afrikaanse kliniese proef biostatistici is nie noodwendig vertroud met al die onderwerpe wat van toepassing is op hul dissipline nie. Die gebiede waarmee hulle die minste vertroud was, was die wetlike vereistes en internasionale riglyne, statistiese analise oorwegings, verslaglewering, en kwaliteitskontrole en dokumentasie. Afgesien van die kennis van statistiese metodes wat deur studie aan universiteite verkry is, is kennis en ondervinding hoofsaaklik deur indiensopleiding, self-studie en eie nalees verkry.

Dit word gehoop dat die implementering van 'n universiteitsprogram spesifiek gemik op kliniese proef biostatistici, verbeteringe aan statistiekkursusse wat tans aangebied word, die ontwikkeling van 'n handleiding vir kliniese proef biostatistici en die totstandkoming van 'n program vir die sertifisering van mediese statistici daartoe sal lei dat dit waarna Kettenring verwys as hy skryf: "Industry needs holistic statisticians who are nimble problem solvers" waar sal word.

ABBREVIATIONS

ASA	American Statistical Association
CFR	Code of Federal Regulations
CRF	Case report form
CRO	Contract research organisation
DSMB	Data Safety Monitoring Board
EFSPI	European Federation of Statisticians in the Pharmaceutical Industry
GCP	Good Clinical Practice
GSOP	Guideline to Standard Operating Procedure
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Affairs
NGO	Non-governmental Organisation
PSI	Statisticians in the Pharmaceutical Industry
SAP	Statistical Analysis Plan
SASA	South African Statistical Association
WHO	World Health Organisation
WHO-DD	WHO – Drug Dictionary

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CHAPTER 1: INTRODUCTION AND RESEARCH OBJECTIVES

1.1 INTRODUCTION

1.1.1 Background

Clinical trials comprise a substantial set of related steps, starting with study design (including protocol writing, case report form (CRF) design and randomisation) and regulatory submission, continuing through the clinical conduct of the study, data management and statistical analysis, and culminating in the reporting of the study results. In recent years the importance of biostatistical input into these steps has been recognised, and such input has been made mandatory by regulatory agencies (International Conference on Harmonisation (ICH), 1996b; ICH, 1998b and Department of Health, 2000). This regulation has resulted in an increasing number of statisticians being employed in the pharmaceutical industry and by regulatory authorities where statisticians review applications for the marketing approval of medicinal products (Köpcke, Jones, Huitfeldt and Schmidt, 1998).

Clinical trials are often categorised according to the phase of drug development in which they are performed, i.e. Phase I to Phase IV trials. Senn (1997) gives the following definitions for clinical trials in each of these phases:

- Phase I trials – The first studies in man. Often, but not exclusively carried out in healthy volunteers. Pharmacokinetics of the drug and basic tolerability information are often obtained from these studies.
- Phase II trials – The first attempts to prove efficacy of a treatment. These trials are often the first studies in patients. Dose finding is a common objective of such studies.
- Phase III trials – Large-scale 'definitive' studies including control groups carried out once probable effective and tolerated doses of the drug have been established, with the object of proving that the drug is suitable for registration.
- Phase IV trials – studies undertaken either after registration or during registration with the purpose of discovering more about the drug, often with respect to safety but sometimes to examine efficacy in different populations.

Such studies are often larger and simpler than regulatory studies and may lack a control group.

1.1.2 Industry growth

The clinical trial industry in South Africa has grown substantially over the recent years with an estimated growth of 40% from 1997 to 1998 (Christley, 1998). This growth has continued with an estimated yield of R826 million in 2000 (Department of Health, 2000). Together with the growth of this industry, there has been an increase in the number of statisticians working as clinical trial biostatisticians in South Africa.

1.1.3 Acknowledgement of role of clinical trial biostatisticians in clinical trials

The Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa (Department of Health, 2000) specify that statisticians should have an advisory and operative function in the steps involved in a clinical trial. These guidelines also state that, "the protocol and the final study report should be reviewed and commented upon by a statistician".

The guidance document mentioned above specifies that sponsors of clinical trials should use "appropriately qualified individuals" throughout all stages of the trial process. This broad requirement for all personnel involved in clinical trials is supported by the ICH E6 Good Clinical Practice (GCP) guideline (1996b) which includes the principle that: "Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)". The ICH E9 guidance on Statistical Principles for Clinical Trials (1998b) is more specific regarding the requirements for the clinical trial biostatistician, "... it is assumed that the actual responsibility for all statistical work associated with clinical trials will lie with an appropriately qualified and experienced statistician, as indicated in ICH E6. The role and responsibility of the trial statistician, in collaboration with other clinical trial professionals, is to ensure that statistical principles are applied appropriately in clinical trials supporting drug development. Thus, the statistician should have a combination of education/training and experience sufficient to implement the principles articulated in this guidance".

1.1.4 Qualifications and experience

These guidelines lead to the question about what constitutes an "appropriately qualified and experienced" biostatistician? After investigating the European pharmaceutical industry a working group of the European Federation of Statisticians in the Pharmaceutical Industry (EFSPI) sought to document the range of qualifications and experience of individuals regarded as "qualified statisticians" in European countries affiliated with the EFSPI; furthermore, the working group sought to establish if it was feasible to develop guidelines for "qualified statisticians" (EFSPI Working Group, 1999). The working party agreed that a "qualified medical statistician" is expected to have a university degree in statistics, or equivalent, plus more than three years of experience in medical statistics. However, the working party conceded that this definition was vague since it lacked detail regarding the content of university courses.

Phillips (1999) specified the qualifications and experience required from statistical personnel in Phase II/III clinical research for different levels of responsibility, as outlined in Table I.

Table 1: Qualification and experience for different levels of statistical personnel in Phase II/III clinical research

Title	Qualification	Experience (years)	Level of Responsibility
Statistician	BSc	-	Study [a]
Senior Statistician	MSc, PhD	≥ 5 years	Project [b]
Principal Statistician	MSc, PhD	≥ 10 years	Therapeutic Area [c]

[a] Comprises the analysis of clinical data and coauthorship of final study reports.

[b] Comprises the analysis of clinical data and coauthorship of final study reports, as well as involvement with the statistical aspects of planning individual clinical studies.

[c] Comprises overall statistical support for one or more clinical projects from inception to completion.

1.1.5 Desirable traits of clinical trial biostatisticians

Chuang-Stein (1996) summarised the desirable traits of a clinical trial biostatistician and discussed the on-the-job training of a graduate statistician for developing these traits. It was suggested that, aside from sound training in statistical theory, a statistician should know the basic elements of both drug development and relevant therapeutic areas. Statisticians should know

regulatory requirements for drug approval, remain up-to-date with the computer facilities relevant to their area of support, and develop the skills required for the effective communication of statistical concepts and ramifications. These traits are similar to the skills of an effective industrial statistician as listed in an American Statistical Association (ASA) report by the Committee on Training of Statisticians for Industry's Section on Statistical Education (1980).

1.1.5.1 The drug development process and clinical trials

Amongst the characteristics of a clinical trial biostatistician Chuang-Stein (1996) mentions "understanding elements of the drug development process". Drug development includes conducting a sequential process of preclinical testing and a series of clinical trials (Karlberg, 1998). Altman (1991) defines a clinical trial as a planned experiment on human beings which is designed to evaluate the effectiveness of one or more forms of treatment. Altman continues that clinical trials merit special attention due to their medical importance, mentioning problems in design and analysis, and specific ethical issues. In order to practice as a clinical trial biostatistician a statistician should be familiar with drug development and the rationale and conduct of a clinical trial.

A clinical trial biostatistician is part of a large multidisciplinary project team and teamwork is essential to be successful in clinical research (Phillips, 1999). Thus the clinical trial biostatistician should be familiar with the personnel involved in a clinical trial and their responsibilities.

1.1.5.2 Regulatory requirements and international guidelines

The marketing of any new medicinal product requires the regulatory approval of the appropriate governmental authority (Lewis, Jones and Rohmel, 1995). Similarly, even the conduct of clinical trials with as yet unapproved medicinal products requires regulatory approval. To provide direction to sponsors in the design, conduct, analysis and evaluation of clinical trials, regulatory authorities have issued guidelines that are partially or entirely concerned with biostatistics (Phillips, Ebbutt, France and Morgan, 2000).

The most recent and comprehensive biostatistical guideline is the ICH E9 guideline (1998b) "Statistical Principles for Clinical Trials". This guideline was developed using existing biostatistical guidelines from Europe, the United States and Japan and input from an ICH expert working group. The guideline has been adopted by the regulatory authorities in Europe, the United States and Japan (Phillips et al, 2000).

Other ICH guidelines are not directly concerned with biostatistics but are concerned with the conduct of clinical trials and the development strategy for new medicinal products and refer to statistical concepts; as such a clinical trial biostatistician should be familiar with these guidelines:

- E1 – The Extent of Population Exposure to Assess Clinical Safety (ICH, 1994a)
- E2A, E2B and E2C – Clinical Safety Data Management (ICH, 1994b; ICH, 1997a and ICH, 1996a)
- E3 – Structure and Content of Clinical Study Reports (ICH, 1995)
- E4 – Dose-Response Information to Support Drug Registration (ICH, 1994c)
- E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH, 1998a)
- E6 – GCP: Guideline for Good Clinical Practice (ICH, 1996b)
- E7 – Studies in Support of Special Populations: Geriatrics (ICH, 1993)
- E8 – General Considerations for Clinical Trials (ICH, 1997b)
- E10 – Choice of Control Group in Clinical Trials (ICH, 2000a)
- E11 – Clinical Investigations of Medicinal Products in the Pediatric Population (ICH, 2000b)

In addition to the ICH E9 guideline, the E3, E6 and E10 guidelines are considered most applicable to the clinical trial biostatistician.

The South African Department of Health developed "Guidelines for good practice in the conduct of clinical trial in human participants in South Africa" (2000). The purpose of these guidelines is to provide South Africa with clearly articulated standards of good clinical practice in research that are also relevant to local realities and contexts.

Statisticians in the Pharmaceutical Industry (PSI), a United Kingdom based association, developed a set of twelve guidelines for standard operating procedures (GSOPs) to provide detailed guidance on good statistical practice in clinical research (North, 1998). The GSOPs are generic in nature and are updated periodically to maintain consistency with ICH guidelines and other appropriate documents. Although clinical trial biostatisticians are required to follow any standard operating procedures specific to their employers it is advisable that they be aware of the content of the GSOPs. The titles of the GSOPs follow (North, 1998):

1. Clinical Development Plans
2. Clinical Trial Protocols and Case Report Forms
3. Statistical Analysis Plans
4. Determination of Availability of Data for Analysis
5. Randomization and Blinding Procedures
6. Data Management
7. Interim Analysis Plans
8. Statistical Reports
9. Archiving and Documentation
10. Data Overviews
11. Quality Assurance and Quality Control
12. Interaction between a Sponsor Company and a Contract Research Organisation (CRO)

Computer system validation in clinical trials is important in order to ensure the credibility of the analysis results. The US Code of Federal Regulations (CFR) Title 21, Part 11 document (2001), "Electronic records; Electronic signatures", addresses this validation issue along with the issue of the ensuring that an audit trail of any data changes exists. Clinical trial biostatisticians should be aware of these issues and ensure that the processes that they follow take them into consideration.

1.1.5.3 Clinical trial design

There is consensus that a clinical trial biostatistician should provide input into the overall design of a clinical trial. Lewis et al (1995) state that statistical considerations are very relevant to the design of much of the scientific work carried out to support clinical trials and emphasise the need for a professional statistical contribution to the design of a clinical trial. DeMets, Anbar, Fairweather, Louis and O'Neill (1994) mention the conceptualisation of a problem or the design of a study as one of the primary responsibilities of a consulting statistician. Effective design equates to better studies, and faster product licenses if the product is effective. In writing about life as an academic medical statistician, Pocock (1995) also encourages consultancy on study design.

1.1.5.3.1 Type of trial, design and outcome variables

Providing input into the design of a clinical trial includes providing recommendations regarding the type of clinical trial (e.g. non-inferiority trial, superiority trial or equivalence trial), the most appropriate clinical trial design (e.g. parallel, cross-over and factorial) and the type of outcome variables to be used (e.g. composite variables and global assessment variables) (ICH, 1998b). In their GSOPs the PSI working party mention the previous considerations as well as others such as ensuring the timing and frequency of assessment are appropriate (North, 1998).

1.1.5.3.2 Sample size

Donahue (2000), in jest, relates one of the questions he, as a statistician, has been asked, "I am planning a new trial with this design. How many patients do I need? Oh yeah, and the budget only allows for 60 patients in each treatment group." One of the areas in which clinical trial biostatisticians provide input into clinical trials is by calculating sample sizes. Sample size calculation is tricky since it requires assumptions about variances and differences to be detected but also rates of dropouts, loss to follow-up and accrual rates (Ellenberg, 1990).

1.1.5.3.3 Protocol

Many of the statistical considerations involved in reviewing a clinical trial protocol are previously discussed, such as the design of a clinical trial and sample size calculation. A clinical trial biostatistician should review the entire protocol and be aware of relevant literature, the clinical development plan and similar trials (North, 1998). A statistician should ensure the protocol appropriately addresses issues of randomisation and blinding and minimises sources of bias as much as possible. The details of the planned statistical analysis should be reviewed to ensure they are correct and issues of multiplicity, handling of dropouts, sample size revisions and the testing of relevant assumptions are suitably addressed (Phillips, 1999).

1.1.5.3.4 Randomisation

The randomisation schedule of a clinical trial documents the random allocation of treatments to patients (ICH, 1998b). A clinical trial biostatistician is often involved in the preparation of the randomisation materials. These materials may include the preparation of a randomisation schedule or list, detailing which patient will receive which treatment or which treatment sequence, generation of a randomisation dataset and the printing of code-break envelopes. ICH E9 (1998b) details some statistical considerations regarding randomisation such as the choice of block size, stratifications and ensuring limited access to the randomisation schedule. North (1998) also mentions these considerations and others along with suggested procedures for conducting randomisation in the guideline for a standard operating procedure on randomisation and blinding procedures.

1.1.5.3.5 Case report form (CRF)

A CRF should only include relevant items which will be evaluated for the final report (North, 1998). When clinical trial biostatisticians review CRFs they can ensure that all essential information is collected and make a case for not collecting nonessential information (Monti, 2001). Grobler, Harris and Jooste

(2001) include suggestions of how a clinical trial biostatistician can contribute to the CRF design:

- Balancing effective data collection with simple data entry.
- Ensuring the design of the CRF facilitates the final statistical programming through efficient data structuring and including coded fields rather than free-text.
- Ensuring all and only necessary data are collected.
- Ensuring that raw data rather than calculated data are included in the CRF.
- Ensuring that the CRF for trials in the same program are similar enough to facilitate combining data over trials.

1.1.5.3.6 Interim Analysis

An interim analysis is any examination of the data prior to locking the database of a clinical trial for the final analysis (North, 1998). Interim analyses and data monitoring are commonly employed during clinical trials of treatments of life-threatening disease, severely debilitating illness or during trials with long-term follow-up (Pong and Chow, 1997). The major concerns regarding interim analysis and data monitoring are the potential bias of the estimated treatment effect, the inflation of the false negative rate and the documentation of the process. Thus a clinical trial biostatistician should make an effort to ensure that known and unknown biases are minimised or eliminated. The PSI GSOP, "Interim Analysis Plan", covers the procedures to be followed when conducting an interim analysis (North, 1998). The ICH E9 guideline (1998b) requires that all interim analyses are described in full in the clinical study report.

1.1.5.4 Data management

A clinical trial biostatistician should provide input into the data management processes in a clinical trial (Monti, 2001). This input includes providing recommendations regarding the structure of the database, the data validation specifications and identifying critical data (Grobler et al, 2001). The biostatistician is also expected to conduct a statistical review of a database prior to accepting it for analysis. In order to conduct these tasks the clinical trial

biostatistician should have a thorough understanding of the data management process.

By providing input into the structure of the database a clinical trial biostatistician is able to ensure that the resulting database meets the needs of the statistical programmers and is able to be combined with other databases to facilitate the pooling of data across studies (Erasmus and Schall, 1998).

Database validation is conducted to ensure the completeness and consistency of a database. A statistician can help data managers by providing input into the validation specifications to identify errors early before the data trail is cold. When reviewing the database a statistician can also assess what types of data issues (and their resolutions) might affect the data summaries (Monti, 2001).

1.1.5.5 Statistical analysis considerations

Lewis et al (1995) state, as is widely accepted, that statistical considerations are very relevant to the analysis of clinical trials. One of these considerations is the pre-specification of the statistical analyses, that is specification prior to the unblinding of the treatment assignment. The ICH E9 guideline (1998b) requires that at least the key features of the eventual statistical analysis be written in the statistical section of the protocol. However, it continues to say that a statistical analysis plan (SAP) may be prepared after finalisation of the protocol but prior to unblinding of the data. The preparation of an SAP has become widely supported (Cook, 1995; Phillips, 1999; North, 1998 and Phillips et al, 2000).

1.1.5.5.1 Statistical analysis plan

The SAP is intended to be a detailed description of the methods and presentation of the analysis for each type of data in the study. The SAP is seen as a "contract" between the clinical trial biostatistician and their customer (internal or external) (Phillips et al, 2000). There also seems to be agreement that table templates depicting the planned presentation of the data should be included in the SAP. North (1998) and Phillips (1999) each provide a list of

issues that should be addressed in an SAP. The following are the issues they suggest should be included in an SAP:

- Methods for handling multicentre data, repeated measurements, multiple endpoints and comparisons, missing data and outliers
- Use of baseline values and covariate data
- Rules for calculation derived data
- Analysis of subgroups
- Rules for stopping the trial and allowance for them in the analyses, as well as interim or sequential analyses
- Levels of clinical and statistical significance (one- or two-tailed)
- Methods for point and interval estimation, and for checking model assumptions
- Identification of fixed or random effects models
- Methods for handling withdrawal and protocol deviations.

1.1.5.5.2 Analysis populations

If all subjects randomised into a clinical trial satisfied all entry criteria, followed all trial procedures perfectly with no losses to follow up and provided complete data records, the set of subjects to be included in the analysis would be self-evident – all randomised subjects (Schall and Harris, 1998). However this compliance to the protocol is usually not the case and thus the clinical trial biostatistician has to make a decision as to which patients are to be included in the analysis of the trial results (Senn, 1997). The ICH E9 guideline (1998b) specifies that planned analyses and the determination of which data is valid for analysis should be finalised prior to unblinding the treatment assignments. The guideline suggests that treatments should only be unblinded after a blind review of the data. It is advisable that the clinical trial biostatistician arrange a data review meeting at which the data issues are discussed and the SAP and analysis populations are finalised.

1.1.5.5.3 Types of data

Different types of data are collected during a clinical trial. The most commonly identified types are efficacy data and safety data. The data collected in order to evaluate efficacy varies from trial to trial and depends on the trial objectives and the therapeutic area under investigation. The most common safety data collected during a trial are the results from clinical laboratory examinations, adverse events and clinical examinations (including vital signs, physical examinations, x-rays and electrocardiograms). Other types of data that are collected are demographic and background data on the patient and patient disposition data (e.g. treatment compliance and completion data). In addition, any medications taken during or prior to the trial, any relevant medical history and any ongoing concomitant illnesses are also reported for each patient. Each of these types of data needs to be analysed and presented appropriately.

1.1.5.5.4 Analysis issues

The ICH E9 guideline (1998b) includes the prespecification of the analysis and analysis sets, discussed previously, as data analysis considerations. However, it goes on to mention the following topics to be considered during the data analysis: missing values, outliers, data transformation, estimation, confidence intervals, hypothesis testing, adjustment of significance and confidence levels, subgroups, interactions and covariates. Phillips et al (2000) clarify the practical implementation of some of these issues. Pong and Chow (1997) discuss similar issues and mention that many of them should be discussed in the final clinical study report.

1.1.5.5.5 Pharmacokinetics and pharmacodynamics

Pharmacokinetics and pharmacodynamics are often described as "what the body does to the drug" and "what the drug does to the body", respectively. According to Senn (1997) clinical pharmacokinetics is a science important to all clinical trial biostatisticians. However, though statisticians primarily working in Phase I and II trials seem to have a good understanding of pharmacokinetics and pharmacodynamics, statisticians working in the latter phases seem to have

little knowledge of these topics. Another subset of Phase I trials is bioequivalence trials which investigate the equivalence of the test and reference product and thus avoid the need for full clinical development (Senn, 1997). As for pharmacokinetics the analysis of these trials follow accepted analysis methods. In order to be responsible for the analysis of such studies a clinical trial biostatistician should understand the requirements associated with this topic.

1.1.5.5.6 Coding

International coding dictionaries are used to code adverse event, medical history, concomitant illness and medication data. In order to appropriately analyse, present and interpret the data a clinical trial biostatistician should have an understanding of the structure of such a dictionary and how terms are coded using it. The following are the most commonly used dictionaries:

- MedDRA (ICH, no date) – Medical Dictionary for Regulatory Affairs: This dictionary is used to code diseases, diagnoses and investigations. This is a trademark of the dictionary compiled by the International Federation of Pharmaceutical Manufacturers Association.
- ICD-9 (Centre for Disease Control, no date-a) and ICD-10 (Centre for Disease Control, no date-b) – International Classification of Diseases, Revisions 9 and 10: This dictionary is used to code medical history, concurrent illnesses and non-drug therapy. The dictionary is the World Health Organisation's (WHO) classification of diseases.
- WHO-DD – WHO Drug Dictionary (World Health Organisation, no date): The dictionary is used to code medications and is maintained by the WHO, Collaborating Centre for International Drug Monitoring.

1.1.5.5.7 Analysis datasets

A clinical trial biostatistician contributes to the format of the datasets received from data management. However, these master datasets often have to be modified to create analysis datasets to use in generating tables and analyses (Monti, 2001). North (1998) mentions the requirement that all analysis datasets

derived from the master database should be checked to ensure they contain the intended data. In order to perform this validation the clinical trial biostatistician should prepare specifications detailing the intended content of the derived dataset. Keeping the specifications for derived datasets consistent over different studies will facilitate efficiencies such as the re-use of programming code (Monti, 2001). The Clinical Data Interchange Standards Consortium database standards have been developed for the industry to assist this process of standardisation (CDISC Inc., no date). A clinical trial biostatistician should be aware of how to implement these standards when analysing a clinical trial.

1.1.5.6 Statistical methods

Although clinical trial biostatisticians need to have a wide knowledge of the industry in which they are applying statistical methodology they also should be able to apply statistical principles and methods appropriately to clinical trials (DeMets et al, 1994). The EFSPI Working Group (1999) includes the requirement for a strong technical foundation amongst the skills and knowledge needed by a statistician in the pharmaceutical industry. This Working Group agree that a university degree in statistics should be sufficient to provide a clinical trial biostatistician with this technical foundation. Chuang-Stein (1996) supports this view mentioning that it is well-accepted that clinical trial biostatisticians should have a sound theoretical background and the best place to acquire this knowledge is in a graduate program.

Both the EFSPI Working Group (1999) and Chuang-Stein (1996) mention that although a degree in statistics is sufficient theoretical training for a clinical trial biostatistician, such a statistician should be continuously updated on the recent advancements in methodology relevant to his/her area of support in the drug development process.

1.1.5.7 Reporting

The clinical trial report is a document containing an overview of the study and the clinical and statistical findings (Phillips, 1999). There seems to be consensus regarding the role of a clinical trial biostatistician in the clinical trial reporting process. According to the ICH E9 guideline (1998b) the clinical trial

biostatistician is one of the team finally responsible for the clinical trial report. Cook (1995) includes writing up the study results and drawing conclusions from these results under the role of a biostatistician during/after a clinical trial. Phillips (1999) supports this view saying that a clinical trial biostatistician has a coauthorship responsibility on a clinical trial report.

Given the authorship responsibility a clinical trial biostatistician should be familiar with the ICH E3 guideline (1995) which describes the structure and content of a clinical trial report. The clinical trial biostatistician should also ensure the accurate interpretation of the statistical output and correct description of analytical issues and data handling requirements in the final report.

Pocock (1995) mentions that as a member of the collaborative research team the statistician should have an authorship responsibility on publications rather than just being acknowledged. As such a statistician should be familiar with writing and reviewing publications. There are some main principles and conventions that guide scientific style in clinical fields. Any author, including a statistician, should be familiar with these conventions in order to write both clinical study report and publications effectively (Huth, 1990).

1.1.5.8 Quality control and documentation

Quality control and review procedures need to be implemented by the clinical trial biostatistician to ensure accurate representation of the data and results. To assure quality a clinical trial biostatistician should ensure that appropriate standard operating procedures are in place before conducting any trial-related activities (ICH, 1996b). GCP also requires that quality control should be applied at each stage of data handling to ensure that all data are reliable and have been processed correctly. A further requirement is that the sponsor should ensure that appropriate individuals are involved in all stages of the trial processes from designing the protocol to the final clinical trial report.

In their GSOPs designed to ensure good statistical practice (North, 1998), the PSI Professional Standards Working Committee interpreted these broad requirements in terms of the responsibility of the clinical trial biostatistician:

- The documentation should indicate that a statistician was involved in the design, review and approval of the trial protocol, randomisation list, CRF, database design and the reports.
- The documentation should indicate that the clinical trial biostatistician reviewed the data presentations and analysis interpretations, ensuring that the presentations were unambiguous, assumptions are clearly stated and limitations understood.
- The clinical trial biostatistician should ensure the accuracy and validity of computer programs used in the statistical analyses; and keep a full record of all computer programs used.

According to North (1998) all aspects of clinical trials must be documented and this documentation should be retained in an archive. The archived documentation provides evidence of the conduct and findings of the trial and should be sufficient to allow the reconstruction of the project. The archived documents should include hardcopies of relevant documents as well as the database and all relevant programs. Details of the computer hardware and software needed to reconstruct the project electronically should be retained. These documents should be available for audits or inspection by the regulatory authority(ies) (ICH, 1996b).

1.1.5.9 Computer skills/packages

According to Cook (1995) one of the roles of a clinical trial biostatistician is to write the analysis programs. This opinion is supported by DeMets et al (1994) who advocate that the knowledge of computer software for analyses and data management is essential. Liss (2003) and Chuang-Stein (1996) also both include computer skills as necessary for an effective clinical trial biostatistician. However, Pocock (1995) disagrees suggesting that such tasks can be handled by less qualified assistants.

The following software packages are commonly used by clinical trial biostatisticians in the pharmaceutical industry:

- SAS® (SAS Institute Inc, no date) is regarded as the software package of choice for the analysis of clinical trials in the pharmaceutical industry.
- Programs such as Microsoft Word® and Excel® are used extensively for the presentation of results.
- Microsoft PowerPoint® is most often used when making formal presentations.
- NQuery® (Statistical Solutions Inc, no date) is a software package used to perform sample size calculations.
- StatXact® (Cytel Software Corporation, no date) provides access to exact statistical inferential methods not available in SAS®.
- WinNonLin® (Pharsight Corporation, no date) is a software package used to calculate pharmacokinetic parameters.
- CIA® (Gardner and Altman, 1989) is used to calculate confidence intervals.

1.2 RATIONALE

An understanding of the profile (education/training, knowledge, years of experience, part of the industry in which they are employed) of clinical trial biostatisticians internationally and how biostatisticians in South Africa compare with this profile will yield many benefits. It will enable employers to recruit and train new biostatisticians effectively and to develop their existing biostatisticians in any areas where training needs may be identified. Individual biostatisticians will be able to identify topics in which to undergo further training, if necessary.

An assessment of the training needs of clinical trial biostatisticians in South Africa and how these needs compare to what is offered at South African universities will enable the universities to identify how they can better serve medical research and the pharmaceutical industry. This research can also contribute to the development of an outline to a comprehensive manual or training programme to accommodate the learning needs of a clinical trial biostatistician and may subsequently be used in either a university or business context.

1.3 RESEARCH QUESTIONS

What is the profile of clinical trial biostatisticians in South Africa; and what resources are available in South Africa to train an appropriately qualified and experienced biostatistician? How does what is available in South Africa compare to what literature defines as an appropriately qualified and experienced clinical trial biostatistician and the profile of biostatisticians internationally?

1.4 RESEARCH OBJECTIVES

The objectives of this thesis are to:

- Describe what constitutes an appropriately qualified and experienced clinical trial biostatistician, as reflected in literature.
- Document the profile (education/training, knowledge, years of experience and part of the industry in which they are employed) of biostatisticians internationally, as reflected in literature, and how clinical trial biostatisticians in South Africa compare to this profile.
- Investigate which of the characteristics of an appropriately trained and experienced biostatistician are met by biostatisticians in South Africa, and how South African biostatisticians acquired their knowledge (university degree, on-the-job training, formal corporate training, self-study/reading).
- Investigate what statistical and biostatistical training is offered at universities in South Africa.
- Compile an outline of a comprehensive manual/training programme to be developed in order to train clinical trial biostatisticians.

1.5 TERMINOLOGY

Clinical trial: Spilker (1991) defines a clinical trial as a subset of those clinical studies that evaluate investigational medicines in Phases I, II and III, where clinical studies are that class of all scientific approaches to evaluate medical disease prevention, diagnostic techniques, and treatments.

Clinical trial biostatistician: The ICH E9 guideline (1998b) defines a trial statistician as a statistician who has a combination of education/training and experience sufficient to implement the principles in the guideline and who is responsible for the statistical aspects of the trial. However, for the purpose of this thesis a clinical trial biostatistician will refer to a statistician responsible for providing statistical input at any stage of a clinical trial, from the design through to the final study report. The biostatistician may be employed at a variety of facilities such as pharmaceutical companies, university research or statistical departments, CROs and regulatory authorities, or they may consult privately. Furthermore for the purpose if this thesis a clinical trial biostatistician is defined as a statistician who analysed at least one clinical trial per year. Statisticians not meeting this criterion were excluded from the data summaries.

CHAPTER 2: RESEARCH DESIGN AND METHODOLOGY

The research design comprised three components: a literature study, a questionnaire survey of the profile of clinical trial biostatisticians in South Africa, and a survey of the content of university statistics courses in South Africa.

2.1 LITERATURE STUDY

A literature study was performed to investigate how literature defines an "appropriately qualified and experienced biostatistician". Furthermore, literature was consulted regarding which training/education issues are important for a clinical trial biostatistician, to ensure that these topics were included in the questionnaire survey. The literature sources included journals from statistical, medical and pharmaceutical fields of study, books on medical statistics and clinical trial methodology, applicable national and international guidelines and examples from clinical trials.

A literature search was done covering the journals most relevant to the topic being researched. The timeframe of interest was mostly from 1990 to present. The keywords that were used for the search were: biostatistician, statistician, training, experience, development, qualifications, career, performance, curriculum. The journals which were considered of most interest were: Biometrics, British Medical Journal, Statistics in Medicine, Applied Clinical Trials, Controlled Clinical Trials, The American Statistician, Journal of the Royal Statistics Society, Biometrika, Controlled Clinical Trials, Journal of Biopharmaceutical Statistics, Biostatistika and the Drug Information Journal.

2.2 SURVEY OF PROFILE OF CLINICAL TRIAL BIOSTATISTICIANS

2.2.1 Research design

A questionnaire survey was designed to investigate the profile of clinical trial biostatisticians in South Africa. The questionnaire was designed to assess the knowledge of respondents in areas about which appropriately educated/trained clinical trial biostatisticians should have knowledge and to collect information on how they acquired this knowledge (university degree, on-the-job training, formal corporate training, self-study/reading).

2.2.2 Research population and sampling

A critical factor in obtaining quality survey findings is in locating all members of the population under study, to ensure they all have the opportunity to be sampled (ASA, 1997a).

2.2.2.1 Clinical trial biostatisticians

The sampling frame for this questionnaire survey was intended to include all clinical trial biostatisticians in South Africa. The ICH E9 guideline (1998b) defines a trial statistician as a statistician who has a combination of education/training and experience sufficient to implement the principles in the guideline and who is responsible for the statistical aspects of the trial. However, for the purpose of this thesis a clinical trial biostatistician will refer to a statistician responsible for providing statistical input at any stage of a clinical trial, from the design through to the final study report, who analysed at least one clinical trial per year. The biostatisticians may be employed at a variety of facilities such as pharmaceutical companies, university research, statistical or medical departments, CROs and regulatory authorities, or they may consult privately.

2.2.2.2 Establishing a sampling frame

To establish a sampling frame various institutions were approached that might employ or come into contact with clinical trial biostatisticians; the institutions consisted of: pharmaceutical companies, university research or statistics/mathematical statistics departments, university medical faculties or pharmacy departments, CROs, regulatory authorities and other governmental research organisations. In order to include in the sampling frame clinical trial biostatisticians that possibly consult privately the candidate approached individuals on the South African Statistical Association (SASA) Consultant List (SASA, 2003). Appendix A contains a list of institutions that were contacted to identify clinical trial biostatisticians.

2.2.2.3 University research and statistics departments

A list of university statistics departments with contact details was found in the SASA newsletter (June 2002). Heads of Departments at these institutions were contacted in order to identify clinical trial biostatisticians. Contact was made by means of a letter explaining the purpose and possible benefits of the survey, defining what a clinical trial biostatistician was in the context of the survey and asking for contact details of possible clinical trial biostatisticians. A copy of the letter by which contact was made is included in Appendix B. The letters were distributed by post. The Heads of Department were provided with a self-addressed postage-paid envelope in which to place their response, they were also given the option of providing response by email or facsimile.

Of the 21 original contacts that were made, 15 (71.4%) responses were received. Contacts were followed-up three times or until response. Of the 15 responses, only 5 provided details of clinical trial biostatisticians known to them and the others indicated that they were not aware of individuals that fit the profile of clinical trial biostatisticians.

2.2.2.4 University medical faculties or pharmacy departments

A list of university medical faculties and pharmacy departments was sourced from the Purchasing Consortium Southern Africa's diary (2003). Deans of medical faculties and Heads of Departments of pharmacy departments were contacted in order to identify clinical trial biostatisticians. A copy of the letter by which contact was made is included in Appendix B. The letters were distributed by email consisting of a short message provided in the body of the email and the letter included as an attachment. Contacts were given the option of providing response by email, facsimile or post. All responses were received by email.

Of the 14 faculties contacted, ten (71.4%) responses were received. The contacts were followed-up three times or until response. Of the ten responses, four provided details of clinical trial biostatisticians and the others indicated that they did not know any clinical trial biostatisticians.

2.2.2.5 Contract research organisations

Few CROs providing biostatistical services exist within South Africa, thus those known to the candidate and her supervisors through professional exposure and interaction were included in the sampling frame. Biostatisticians known to the candidate and heads of departments within various institutions were contacted in order to identify clinical trial biostatisticians. A copy of the letter by which contact was made is included in Appendix B. A letter was distributed by email consisting of a short message provided in the body of the email and the letter included as an attachment. Contacts were given the option of providing response by email, facsimile or post. All responses were received by email.

Four companies were contacted:

(i) One company indicated that although their organisation employed clinical trial biostatisticians they were not willing to participate in the survey. The company is known to employ four clinical trial biostatisticians.

(ii) One company provided details of one clinical trial biostatistician,

(iii) One company provided contact details for two clinical trial biostatisticians, but indicated that they operated as a non-governmental organisation (NGO) rather than a CRO

(iv) One company provided contact details for nine clinical trial biostatisticians.

2.2.2.6 Regulatory authorities

The Department of Health and the Medicines Control Council were contacted to establish if any clinical trial biostatisticians were employed in a regulatory role. Human resource and information officers within the institutions were contacted in order to identify clinical trial biostatisticians. A copy of the letter by which contact was made is included in Appendix B. The letters were distributed by email constituting a short message provided in the body of the email and the letter included as an attachment. Contacts were given the option of providing response by email, facsimile or post. All responses were received by email.

Both institutions responded that they did not employ clinical trial biostatisticians.

2.2.2.7 Government research organisations

The two government research organisations that were contacted were Statistics SA and the Medical Research Council. An information officer at Statistics SA and the Unit Head at the Medical Research Council were contacted in order to identify clinical trial biostatisticians. A copy of the letter by which contact was made is included in Appendix B. The letters were distributed by email consisting of a short message provided in the body of the email and the letter included as an attachment. Contacts were given the option of providing response by email, facsimile or post. All responses were received by email.

Statistics SA responded that they employed statisticians, but none in the role of clinical trial biostatisticians. The Medical Research Council provided names of all the biostatisticians that they employ as well as details for the individuals that they use in a consulting capacity, a total of 17 contacts.

2.2.2.8 Privately employed clinical trial biostatisticians

In order to include clinical trial biostatisticians that might consult privately in the sampling frame the candidate approached individuals on the SASA Consultant List, as provided on the SASA official internet site (SASA, 2003). These individuals were directly included in the sampling frame and thus sent a clinical trial biostatistician questionnaire and asked to inform the candidate if they did not meet the definition of a clinical trial biostatistician.

2.2.2.9 Pharmaceutical companies

One type of employer of clinical trial biostatisticians internationally is pharmaceutical companies. A list of pharmaceutical companies in South Africa was compiled using two sources: an online version of the yellow pages (Telkom Directory Services, 2003) and the MDR 2003 (Snyman, 2003). Any companies which were indicated to be distributors, pharmacies, suppliers or marketers were omitted from the list along with any duplicates. For companies with more than one office in South Africa only the head office was included in the list. Each of the companies on the list was contacted by phone, the nature of the survey explained and inquiries made as to whether or not the company employed any statisticians in South Africa. The inquiries were made regarding

statisticians rather than the more specific "clinical trial biostatisticians" for clarity, thereafter individuals would be asked whether or not they qualified as clinical trial biostatisticians.

Of the 133 companies included on the list, 109 indicated that they did not employ statisticians in South Africa, some indicating that they did employ statisticians within their offices overseas (these statisticians were not taken into account since they are not employed within South Africa). Of the remaining 24 companies contacted, 12 of the telephone numbers did not exist, 9 of the numbers were discovered to be the wrong number and no answer was obtained at the remaining 3 numbers (no answer was obtained even with continued attempts in subsequent weeks).

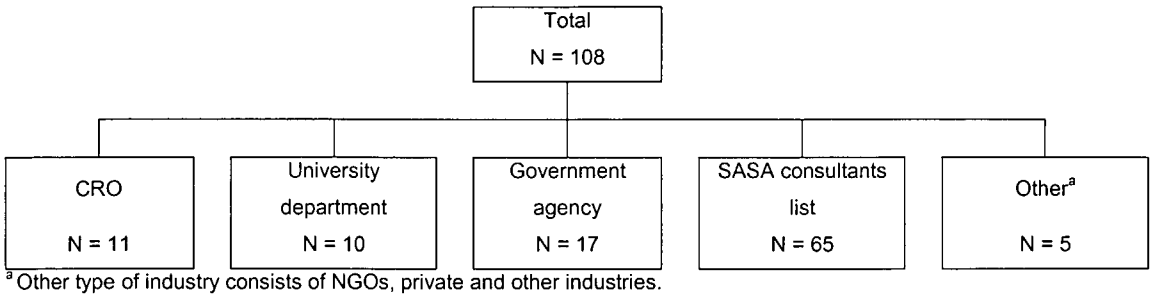
2.2.2.10 Sampling frame reconciliation

The names of possible clinical trial biostatisticians gathered from the different institutions and from the SASA consultants list were reconciled to remove duplicate references to a single person. The candidate and supervisors were not included in the sampling frame.

Due to the small number of clinical trial biostatisticians employed in South Africa the entire population, as identified in the sampling frame, was surveyed. Aside from clinical trial biostatisticians employed by clinical research organisations (see Section 2.2.2.5(i)), the sampling frame was considered to be complete and provide an accurate definition of the population.

The following figure provides an overview of the sampling frame:

Figure 1: Overview of the sampling frame



[a] Other type of industry consists of NGOs, private and other industries.

CRO = Contract Research Organisation

2.2.3 Questionnaire design

The questionnaire was designed to assess, amongst other variables, the knowledge of respondents in areas about which an appropriately educated/trained clinical trial biostatistician should know, and to collect information on how they acquired this knowledge (university degree, on-the-job training, formal corporate training, self-study/reading).

Since this instrument was a self-administered questionnaire, the questions asked and the response options took into consideration that the same information about what is wanted should be conveyed to all the respondents. Thus it was crucial that the concepts were clear and simply expressed, and that information was collected in a manner conducive to the final analysis of the data. The ASA Series on Survey Research Methods includes a pamphlet on designing a questionnaire (1999); the principles mentioned in the pamphlet were applied in the design of the survey.

The questionnaire was designed to be included as an email attachment and to enable respondents to complete the questionnaire electronically. The questionnaire consisted of the following components:

- Introduction and general information
- Instructions on how to complete the questionnaire, including additional instructions on how to complete the questionnaire electronically
- Questions regarding the education and experience profile of the respondent
- Questions regarding the knowledge of the respondents and how they acquired the knowledge

- Abstract and rationale of the research, included as an attachment to the questionnaire

To allow the respondents to complete the questionnaire electronically, check box form fields and text form fields were embedded into the Microsoft Word® version of the questionnaire. A check-box could be crossed by clicking on the check box form field and unchecked by clicking on it a second time. Text could be entered into a text form field by clicking on the field and typing the required text. A copy of the questionnaire is included as Appendix C.

2.2.4 Questionnaire testing

The accuracy and interpretability of the results obtained from a survey depend on effective pretesting of the questionnaire (ASA, 1997c). This step is essential for identifying questionnaire problems relating to the physical design of the questionnaire and the question and term interpretation. Pretesting can be conducted during the questionnaire development stage or during actual administration of the questionnaire. Unfortunately the latter strategy was not feasible due to the small population involved. The pamphlet mentioned above provides 6 methods for conducting pretesting during the questionnaire design phase. Many of these methods are specific to interviewer-lead questionnaires, however one is appropriate to self-administered questionnaires, 'Respondent debriefings'. This method involves a structured follow-up to elicit respondents' interpretations of questions and overall comments on the usability of the questionnaire.

Responder debriefings were performed on 5 individuals who are involved in the clinical trial and biostatistics fields but are not part of the sampling frame, since the population is already small. Care was taken to use individuals who were able to interpret the terminology. Thus, statistical programmers with a university degree with statistics to at least a second year level and more than three years experience were used along with the candidate's supervisors.

Testers were provided with a copy of the clinical trial biostatistician questionnaire to complete, and a copy of a Tester's questionnaire. The tester

version was designed to collect their response to the formatting and content of the clinical trial biostatistician questionnaire, and to collect comments on the overall usability of the questionnaire. A copy of the Tester's questionnaire is included in Appendix D.

Overall the response of the testers to the questionnaire was positive with the exception that the testers indicated that the font type was hard to read and that the font size was too small. This shortcoming was specific to the presentation of the response categories in the Knowledge/Experience section of the questionnaire. The font type was changed and the font size for these categories was increased in the final questionnaire. The question regarding the number of years of experience of a respondent as a clinical trial biostatistician was highlighted as being difficult to quantify and was thus rephrased to inquire as to the respondent's number of years of experience as a statistician (not specifically as a clinical trial biostatistician). An additional question was also included to determine when a clinical trial biostatistician last analysed a clinical trial. One of the testers also suggested the inclusion of a footnote to explain the abbreviation "SOP" (Standard Operating Procedure), and this inclusion was made in the final questionnaire.

2.2.5 Administration and distribution of the survey

Due to the small size of the population being sampled it was imperative to ensure a good response rate to the survey. In the paper "More About Mail Surveys" from the ASA Series on Survey Research Methods (1997b), a list of implementation steps are suggested to encourage survey response. These steps were slightly adapted for the purpose of this survey:

- Using multiple contacts
  - The survey questionnaire was e-mailed to the respondents as an attachment in Microsoft Word® format. The email included a short message to introduce the survey and place it as part of post-graduate research being done through the Department of Biostatistics at the University of the Free State. The survey attachment included a covering letter with further information regarding the survey, the abstract and

rationale of the research and relevant contact details. Respondents were also provided the opportunity to request a hard-copy and self-addressed envelopes in order to complete the survey on hard-copy and return it by post. No respondents requested a hard-copy questionnaire.

- If a respondent did not respond, a reminder was sent to the respondent by email including the respondent's questionnaire as an attachment to the email. A respondent was followed-up until a response was received or to a maximum of four times.
- An acknowledgement email thanking the respondents for their cooperation was sent.

- All emails were personalised and included the candidate's full contact details as a signature.

Once the questionnaire had been completed electronically by the respondent, the respondent was required to save the file including the updates and return it by email, print-it out and return it by fax or post it to the candidate. Most respondents returned their questionnaires by email.

2.2.6 Data entry

Data entry is the process by which the data are entered into a database and checked for accuracy. The data was entered in Microsoft Access®, which allows the capture of structured responses and open-ended textual responses. Two independent data typists entered the data from the questionnaires, in separate databases. A comparison of the double data entry databases was conducted and discrepancies between the two data entries were resolved by consulting the original questionnaire. Only respondent identifiers (no names and addresses, etc) were captured in the database. The data was exported to SAS® for Windows 95/NT (SAS Institute Inc, 1999) to generate the data listings and tabulations, and to conduct the statistical analyses.

2.2.7 Data handling and cleaning

While the questionnaires were being entered various ambiguous and erroneous data were encountered. The following list describes each data anomaly and how it was handled during data entry and/or analysis.

- One respondent did not indicate how knowledge was acquired for the topic within the regulatory requirements and international guidelines section, "21 CFR Part 11 – Electronic records and electronic signatures". However, next to the topic the respondent wrote that she had attended one in-house course in this regard. This information was captured as the respondent having received formal in-house training.
- Two respondents indicated that they were currently employed by a pharmaceutical company. However, it is known that both these respondents work for a CRO; thus the data were analysed as the respondents currently working for a CRO.
- One respondent entered "Other, None" under the industry in which they were previously employed. This field was left blank for other respondents who had not previous worked in other industries.
- Some of the respondents ticked more than one option under the knowledge and experience categories although they were requested to mark only one. In such cases the category which indicated the highest level of knowledge and experience was captured in the database.
- If a respondent did not tick any of the categories under the knowledge and experience category for a specific topic this fact was recorded as "No knowledge/experience" in the database for the relevant topic.
- Any SAS® topics that were recorded under "other appropriate topics" were entered under "Computer skills/packages - SAS".
- One respondent recorded "Other, third year course" under their highest statistics qualification, this fact was entered into the database as a bachelors degree. In South Africa a B.Sc degree in Statistics is a three-year course.
- If the text written next to an "other, specify" field was too long to be entered into the database the text was abbreviated without losing meaning.
- If text was written next to an "other, specify field" but the check box had not be crossed this box was crossed while entering the data.

- The instructions allowed respondents to indicate only a single field under current industry of employment. However, one respondent marked two fields, university research department and private. This data was entered into the database by ticking the "Other" option and specifying "university research department and private.
- One respondent indicated that the year in which they had last analysed a clinical trial was 2004. This response was handled as 2003 in the analyses.
- A respondent indicated under "other" that their highest statistics qualification was two masters degrees. This data was recorded in the database as a masters degree with no information entered under "other, specify".
- If a respondent indicated a method in which they had acquired knowledge or experience without selecting an option under the knowledge/experience category, the knowledge/experience option was left missing.
- A respondent was requested to check only one box indicating their highest statistics qualification. One respondent marked two boxes, "first-year course" and "PhD". This data was entered into the database as "PhD".
- If the last month in which a respondent analysed a clinical trial was recorded on the questionnaire in words this information was converted to the equivalent month in numbers and entered into the database.
- The topics "analysis of continuous data" and "analysis of categorical data" under the statistical methods section were included in the questionnaire as sub-headings. However, in error, check boxes were included alongside these topics in the final questionnaire that was distributed to respondents. The responses to these topics were entered into the database but were not included in the analyses, as the possible interpretation of these topics is not clear.

2.2.8 Data analysis and reporting

Respondents were required to indicate that they analysed at least one clinical trial a year in order to be considered a clinical trial biostatistician and thus be included in the statistical analyses. This criterion resulted in the data for three respondents being omitted from the analyses. Another respondent indicated that he analysed zero clinical trials a year. However, it is known to the

supervisor that the respondent does analyse clinical trials and thus the respondent's data was included in the analyses.

The data was analysed descriptively. Continuous parameters were presented as number of respondents, mean, median, standard deviation and range (minimum and maximum). Categorical data was summarised using contingency tables with absolute and relative frequencies.

Since it was expected that the profile of respondents, the knowledge of the respondents and how they acquired this knowledge could differ according the sphere in which the respondent was employed, a subgroup analysis stratifying by current industry of employment was performed on all the data. There were three subgroups included in the analysis, respondents employed by CROs (10 respondents), respondents employed by university statistics or research departments (9 respondents) and respondents employed by government research agencies (8 respondents).

The subgroup analysis included all but two of the respondents. These respondents are currently employed by an NGO. When these respondents were approached as to which their subgroup was most closely aligned with their current jobs they indicated that their jobs were a combination of the categories provided and thus preferred to form their own subgroup. Since there were only two respondents in this group the subgroup was omitted from the analyses. Note that only one of these two respondents had indicated on their questionnaire that they were employed by an NGO. The other respondent indicated a university research department as the current place of employment. Since it was known that the two respondents worked together it was decided to ask in which group they should be included.

One respondent who currently works both privately and for a university research department was included in the university department subgroup.

2.3 UNIVERSITY COURSE CONTENT SURVEY

2.3.1 Research design

A survey was conducted to establish what undergraduate statistical and biostatistical training is offered at universities in South Africa. In South Africa an undergraduate (bachelors, usually a B.Sc) degree in statistics or related subjects is attained after an equivalent of three-years of full-time study. Thereafter a student may complete a fourth year of study after which a so-called Honours degree is attained (B.Sc Hons).

2.3.2 Research population and sampling

All universities with statistics/mathematical statistics or biostatistics departments in South Africa were surveyed. All other tertiary education facilities were omitted since the preliminary literature search indicated that a clinical trial biostatistician requires at least a university qualification in statistics or a related field (EFSPI Working Group, 1999). Since the number of universities in South Africa is small, all applicable institutions were surveyed rather than choosing a sample (20 universities were approached to participate in the survey).

2.3.3 Recruitment and preparation of participants and distribution of the survey

A letter was sent to the relevant university departments introducing the survey and describing it as post-graduate research being done through the Department of Biostatistics at the University of the Free State (Appendix E). In this mailing the candidate requested copies of the curricula of the undergraduate courses offered by the departments. If there was a lack of response by the department a reminder with contact information to answer general questions about the survey was sent to the department by email. The departments were provided with both stamped pre-addressed return envelopes and electronic contact details to allow them to submit the information with ease. Universities were followed up until response or to a maximum of four times.

2.3.4 Data entry and cleaning

Various definitions of the term "course" are in use by the different South African universities. University courses range from three-month courses to full-year

courses, but all courses are restricted to a specific year of study. Courses were counted as defined by each university and not normalised to be courses of equivalent length.

Each course description was compared to the topics included in the clinical trial biostatistician questionnaire and the topics that each course covered were recorded. This sorting was done independently by the candidate and a PhD statistician with experience of working as both a clinical trial biostatistician and a statistics lecturer. The candidate and supporting statistician compared the topics they had indicated for each course. If there were discrepancies between the assigned topics they were discussed by the parties involved and consensus was reached as to the topics to be included for that specific course. An example of how questionnaire topics were assigned to a specific course is included in Appendix F.

If a course curriculum indicated that the course included the calculation of point estimates, hypothesis tests and confidence intervals it was coded to the analysis of continuous data or categorical data, as appropriate. An additional topic was added to the list namely "Project"; all courses which encompassed data collection, analysis and reporting were coded to this topic. Since many of the courses indicated that they had a computer component without specifying the computer package this component was coded to "Computer usage: package unspecified". If the computer package was specified but was not one of those included in the questionnaire the computer component was coded to "Computer usage: package specified but not in questionnaire list"

The number of courses addressing each specific topic was entered into an MS Excel® spreadsheet per university and per year of study. Two independent data typists entered the data from the coded curriculums, in separate worksheets. A comparison of the double data entry worksheets was conducted and discrepancies between the two data entries were resolved by consulting the original coded course content. Only university identifiers (no names and addresses) were captured in the database. The data was exported to SAS® for

Windows 95/NT (SAS Institute Inc, 1999) to generate the data listings, tabulations, and conduct the statistical analyses.

2.3.5 Data analysis and reporting

The data was summarised descriptively using contingency tables with absolute and relative frequencies.

2.4 ETHICAL CONSIDERATIONS

2.4.1 Ethics Committee Approval

The research proposal along with a copy of the clinical trial biostatistician questionnaire and the letters to be sent to identify clinical trial biostatisticians, to request information from the universities and to inform clinical trial biostatisticians about the survey were submitted to the University of the Free State's Ethics Committee with applicable supporting documentation. The Ethics Committee provided approval for the research to be conducted once the letter to accompany the clinical trial biostatistician questionnaire was translated into Afrikaans and submitted to the committee (ETOVS NUMBER 72/03). The letter was translated and submitted prior to any questionnaires being distributed.

2.4.2 Ethical considerations for the literature study

Ethical publishing practices were adhered to during this research. Mouton (2001) mentions two ethical practices which were implemented during this research: appropriate ascription of authorship to a publication and rejection of any form of plagiarism.

2.4.3 Ethical considerations for the questionnaire survey

The confidentiality of the data supplied by respondents is a well accepted ethical consideration when conducting a survey. The ASA proposes the following policies to safeguard confidentiality (ASA, 1997d):

- Use only number codes to link the respondent to a questionnaire and store the name-to-code linkage information separately from the questionnaires
- Refuse to give the names and addresses of survey respondents to anyone outside the survey organization, including clients

- Destroy questionnaires and identifying information about respondents after the responses have been entered into the computer
- Omit the names and addresses of survey respondents from computer files used for analysis
- Present statistical tables with categories broad enough so that individual respondents cannot be identified.

These policies proposed by the ASA were implemented. It would have been preferable to conduct an anonymous survey, though this was not practical since it is important that there is a high response rate to the survey, and thus there was a need to be able to identify non-responders and follow these up to encourage response.

Participants have the right to full disclosure, which was addressed by ensuring that the participants were informed before participating in the survey by means of an introduction letter discussing the nature of the research and the likely benefits to the participant/industry. The research findings are available to the participants on request in order to allow them to learn from the research and to avoid the results benefiting a single business in the South African Research Industry.

2.4.4 Ethical considerations for the university course content survey

The confidentiality of this data was not an ethical issue in the survey of university course contents since this information is public knowledge.

CHAPTER 3: RESULTS

3.1 SURVEY OF PROFILE OF CLINICAL TRIAL BIOSTATISTICIANS

3.1.1 Response rates

A total of 108 questionnaires were distributed to statisticians. 11 of the questionnaires went to statisticians in the contract research industry, 10 to statisticians working in university departments, 65 to statisticians on the SASA consultants list and 17 to statisticians working for relevant government agencies. The response per category is summarised in the table below (Table 2):

Table 2: Response rates per industry

Industry[c]	Not CTB	Delivery failure	Completed questionnaire	No response	Other[a]	Total
CRO	0	0	11 (100.0 %)	0	0	11
University department	1 (10.0%)	0	7 (70.0%)	2 (20.0%)	0	10
Government agency	5 (29.4%)	0	8 (47.1%)	2 (11.8%)	2 (11.8%)	17
SASA consultants list	12 (18.5%)	35 (53.8%)	3 (4.6%)	9 (13.8%)	5 (7.7%)	65
Other[b]	1 (20.0%)	0	3 (60.0%)	1 (20.0%)	0	5
Total (%)	20 (18.5%)	35 (32.4%)	32 (29.6%)	14 (13.0%)	7 (6.5%)	108

[a] Other response type consists of respondents who left the company during the period the questionnaire was sent out, or was overseas or on sabbatical over this period.

[b] Other type of industry consists of NGOs, private and other industries.

CRO = Contract Research Organisation

Note that the categorisation in Table 2 is based on the categorisation made at the time of the survey distribution and not as per the industry indicated on the questionnaire. All of the CRO statisticians to whom questionnaires were distributed returned completed questionnaires together with most of the statisticians employed by university departments (70.0%). About half of the government agency statisticians to whom questionnaires were sent returned the questionnaires completed with about 30% indicating that they had been incorrectly identified as a clinical trial biostatistician. A high proportion (53.8%) of delivery failures was received for questionnaires sent to individuals on the SASA consultants list with only three statisticians (4.6%) returning completed questionnaires.

As mentioned in the methodology section, three of the respondents who returned questionnaires were deemed not to be currently working as clinical trial biostatisticians since they did not analyse at least one clinical trial a year, and were therefore omitted from the analyses. Thus 29 respondents were considered valid for analysis.

3.1.2 Profile of clinical trial biostatisticians

3.1.2.1 Qualifications

The following table summarises the highest qualifications and the highest statistics qualifications of the respondents (Table 3).

Table 3: Qualifications: Highest qualification and highest statistics qualification (All respondents)

	Qualification	n	%
Highest qualification	Bachelors degree	2	6.9
	Honours degree	7	24.1
	Masters degree	12	41.4
	PhD	8	27.6
	Total	29	100.0
Highest statistics[a] qualification	Bachelors degree	3	10.3
	Honours degree	8	27.6
	Masters degree	10	34.5
	PhD	8	27.6
	Total	29	100.0

[a] Statistics refers to 'statistics', 'mathematical statistics' or 'biostatistics'.

All respondents had at least a bachelors degree in statistics, with 26 (89.7%) having at least a post-graduate statistics degree. Eighteen (62.1%) of the respondents have at least a masters degree in statistics.

A statistics qualification was the highest qualification for the majority of respondents. Two of the respondents had a masters degree in a field of study other than statistics, one of whom had a bachelors degree and the other an honours degree, in statistics.

Clinical trial biostatisticians employed by CROs mostly have honours degrees. In both university departments and government research agencies nearly all respondents have masters degrees and PhDs (Table S.1, Appendix G).

3.1.2.2 Industry

Clinical trial biostatisticians are employed in establishments serving different parts of the pharmaceutical industry. The following table presents the industries in which respondents are currently and were previously employed (Table 4).

Table 4: Current and previous employment by industry (All respondents)

	Industry	n	%
Current employment	Contract research organisation	10	34.5
	University research/statistics department	9	31.0
	Government research agency (MRC, Statistics SA)	8	27.6
	Other, specify[a]	2	6.9
	Total	29	100.0
Previous employment	Pharmaceutical company	1	3.4
	Contract research organisation	7	24.1
	Government regulatory authority (MCC)	1	3.4
	University research/statistics department	12	41.4
	Government research agency (MRC, Statistics SA)	6	20.7
	Private	2	6.9
	Other, specify[b]	2	6.9

[a] The other current industries that were specified are 'University department and Private' and 'NGO'.

[b] The other previous industries that were specified are 'None' and 'UK Ministry of Health'.

Note: A respondent may have been employed in more than one industry previously

The respondents were evenly spread between being currently employed by contract research orgranisations, university departments and government research agencies. None of the respondents were currently employed by pharmaceutical companies.

Regarding previous employment, the most frequent response was university departments, followed by CROs and government research agencies.

Table S.2 (Appendix G) gives the previous industries split by the current sphere in which the clinical trial biostatistician is employed. These results indicate that

most respondents were previously employed in the same part of the industry in which they currently work.

3.1.2.3 Experience

3.1.2.3.1 Years of experience

The following table categorises respondent's years of experience as a biostatistician (Table 5).

Table 5: Years of experience as a biostatistician - not specifically as a clinical trial biostatistician (All respondents)

Years of experience	n	%
<= 5 years	16	55.2
6 - 10 years	3	10.3
11 - 15 years	3	10.3
> 15 years	7	24.1
Total	29	100.0

Over half of the respondents have less than five years of experience. There were three respondents (10.3%) in each of the categories of 6 to 10 years and 11 to 15 years. Almost a quarter of the respondents (7 respondents, 24.1%) have over 15 years of experience of working as a biostatistician.

Between 50% and 60% of the respondents in each of the current industry subgroups had less than 5 years of experience. Three respondents employed in each of CROs and university departments and four respondents in government research agencies have over ten years of experience (Table S.4, Appendix G).

3.1.2.3.2 Percentage of time as a clinical trial biostatistician

The percentage of time the respondents spent working as a clinical trial biostatisticians is given in the table below (Table 6).

Table 6: Percentage of time spent working as a clinical trial biostatistician (All respondents)

Percentage of time as a CTB	n	%
<= 20%	13	44.8
21 - 50%	3	10.3
51 - 80%	5	17.2
> 80%	8	27.6
Total	29	100.0

CTB = Clinical trial biostatistician

Only 8 respondents (27.6%) spent more than 80% of their time working as a clinical trial biostatistician. Another 8 respondents spent between 21% and 80% of their time in this role. Almost half of the respondents (13 respondents, 44.8%) spent less than 20% of their time working on clinical trials.

Most CRO clinical trial biostatisticians indicated that they spend more than 80% of their time as a clinical trial biostatistician, and nearly all spend more than 50% of their time in these activities. In contrast, the majority of university department biostatisticians spend less than 20% of their time as clinical trial biostatisticians. Government research agencies indicate a spread of time spent as a clinical trial biostatistician (Table S.4, Appendix G).

3.1.2.3.3 Number of clinical trials analysed per year

The following table presents the number of clinical trials the respondents analyse in a year (Table 7).

Table 7: Number of clinical trials analysed in a year (All respondents)

Number of clinical trials a year	n	%
<= 3 trials	12	41.4
4 - 6 trials	9	31.0
7 - 10 trials	4	13.8
> 10 trials	4	13.8
Total	29	100.0

The majority of the respondents (21 respondents, 72.4%) analyse up to 6 trials in a year. Clinical trial biostatisticians employed by university departments typically analysed fewer than three clinical trials a year. Those clinical trial

biostatisticians employed by CROs and government research agencies seemed to have a range in the number of trials analysed in a year with a reasonably even spread over the categories. The category with the highest proportion of number of trials per year was four to six trials for CRO biostatisticians (40.0%) and less than three trials for government research agency biostatisticians (37.5%) (Table S.4, Appendix G).

3.1.2.3.4 Experience per clinical trial phase

Clinical trial biostatisticians may have experience in analysing clinical trials in the different phases of drug development. The table below shows the experience of respondents in analysing trials in each of the clinical trial phases (Table 8).

Table 8: Experience in different clinical trial phases (All respondents)

Clinical trial phase	n	%
	(N = 29)	
Phase I	16	55.2
Phase II	16	55.2
Phase III	18	62.1
Phase IV	11	37.9

Note: A respondent may have worked on clinical trials in more than one phase of development

Respondents mostly have experience in analysing Phase III clinical trials and have the least experience analysing Phase IV clinical trials.

The phase of development in which clinical trial biostatisticians had most experience differed according to their current industry of employment. CRO biostatisticians generally had experience in Phase III trials, university biostatisticians in Phase I trials and Government research agency clinical trials in Phase II clinical trials. Although each industry indicated a peak of experience in the phases previously discussed the other phases were reasonably well represented with most categories showing that about half the respondents have experience in each of the other phases. The exceptions to this trend are that university biostatisticians have very little experience in Phase IV trials and

government research agency biostatisticians have less experience with Phase I trials than other phases (Table S.5, Appendix G).

3.1.2.3.5 Task experience

Biostatistical input into clinical trials is required in study design (including protocol writing, CRF design and randomisation), regulatory submission, the clinical conduct of the study, data management and statistical analysis, and in reporting the study results. The following table describes the experience of respondents in performing these tasks (Table 9).

Table 9: Task experience (All respondents)

Task experience	n	%
	(N = 29)	
Writing clinical development plans	1	3.4
Writing clinical trial protocols	14	48.3
Designing case report forms	12	41.4
Statistical analysis of a clinical trial	28	96.6
Writing clinical trial reports	20	69.0
Sample size calculation	22	75.9
Preparation of randomisation materials	13	44.8
Preparation/review of data management plans	16	55.2
Other [a]	1	3.4

Note: A respondent may have experience in more than one task

[a] The other category was specified as the writing of standard operating procedures and the collection, collation and analysis of data for Data Safety Monitoring Boards

Only one respondent had experience in writing clinical development plans. Approximately half of the respondents had experience in most of the tasks involved in clinical trial design. This experience includes writing protocols (14 respondents, 48.3%), designing CRFs (12 respondents, 41.4%), the preparation of randomisation materials (13 respondents, 44.8%) and the preparation and/or review of data management plans (16 respondents, 55.2%). The other task incorporated in clinical trial design is sample size calculation; 22 respondents (75.9%) indicated that they had experience in this activity.

All but one of the respondents indicated that they had experience in the statistical analysis of clinical trials. Experience in the writing of clinical trial reports was noted by 20 respondents (69.0%).

One respondent indicated that they also had experience in tasks other than those listed namely, writing standard operating procedures and the collection, collation and analysis of data for Data Safety Monitoring Boards (DSMBs).

Experience in conducting the various tasks for which a clinical trial biostatistician is responsible is presented by current industry of employment in Table S.3 (Appendix G). Similar task experience rates were observed for most of the tasks regardless of industry of employment. Fewer respondents based at university departments had experience in writing clinical trial reports than at CROs or government research agencies. Respondents employed by CROs had less experience in sample size calculation but more experience in the preparation or review of data management plans than seen in respondents in either university departments or government research agencies.

3.1.3 Knowledge of clinical trial biostatisticians

The clinical trial biostatistician questionnaire was designed to assess, amongst other things, the knowledge of respondents in areas about which appropriately educated and trained to clinical trial biostatisticians should know and to collect information on how they acquired this knowledge (university degree, on-the-job training, formal corporate training, self-study/reading). The topics identified in the questionnaire were grouped into appropriate sections; each of these sections is discussed separately below.

3.1.3.1 The drug development process and clinical trials

Clinical trial biostatisticians require a background to clinical trials, the drug development process and the team involved in conducting clinical trials. The following table covers the level of knowledge/experience respondents in these topics (Table 10).

Table 10: Knowledge/Experience of the drug development process and clinical trials (All respondents)

	No know/exp		Little know/exp		Theoretical know only		Working knowledge		Extensive experience	
Topic	n	%	n	%	n	%	n	%	n	%
History and rationale of RCT	3	10.3	1	3.4	6	20.7	15	51.7	4	13.8
Drug development process	9	31.0	5	17.2	9	31.0	5	17.2	1	3.4
Conduct of a clinical trial	2	7.1	2	7.1	3	10.7	19	67.9	2	7.1
Clinical trial team	3	10.3	7	24.1	4	13.8	12	41.4	3	10.3

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience'

Know = Knowledge, Exp = Experience, RCT = Randomised clinical trial

Twenty-five respondents (86.2%) had at least a theoretical knowledge of randomised clinical trials. However, only 15 respondents (51.6%) had at least a theoretical knowledge of the drug development process. Twenty-four (24) respondents (85.7%) indicated at least a theoretical knowledge concerning the clinical conduct of a study and 19 respondents (65.5%) indicated that they had at least a theoretical knowledge of the clinical trial team, i.e. the personnel involved in conducting a clinical trial and their responsibilities.

More CRO biostatisticians had at least a theoretical knowledge in all four of these topics compared to university and government research agencies (Table S.6a, Appendix G).

Table 11: Method of acquiring knowledge/experience regarding the drug development process and clinical trials (All respondents)

	University degree		On-the-job training		Formal in-house train.		Self-study/ reading		Other train. course(s)	
Topic	n	%	n	%	n	%	n	%	n	%
History and rationale of RCT	7	24.1	16	55.2	7	24.1	11	37.9	1	3.4
Drug development process	3	10.3	9	31.0	6	20.7	8	27.6	1	3.4
Conduct of a clinical trial	5	17.2	18	62.1	9	31.0	12	41.4	1	3.4
Clinical trial team	3	10.3	21	72.4	5	17.2	7	24.1	1	3.4

Note: Train. = Training, RCT = Randomised clinical trial

A respondent could indicate more than one method of acquiring knowledge/experience in a specific topic

Knowledge in all four of these topics was typically acquired through on-the-job training, followed by self-study and reading and then formal in-house training (Table 11). Only one respondent became familiar with these topics through an

external training course. Knowledge in the history and rationale of clinical trials was acquired through a university degree for seven respondents (24.1%) and in the drug development process and the clinical trial team by three respondents (10.3%) each and in the conduct of clinical trials by five respondents (17.2%).

The methods of acquiring knowledge differed in the subgroups. Clinical trial biostatisticians working in CROs mostly acquired their knowledge through on-the-job training and formal in-house training and to a lesser extent self-study and reading. University biostatisticians learned through on-the-job training and government research agencies primarily learned through self-study and reading followed by on-the-job training (Table S.6b, Appendix G).

3.1.3.2 Regulatory requirements and international guidelines

The results of clinical trials are submitted to regulatory authorities in order to obtain registration for the drug or treatment in the relevant country or countries. The following table summarises the familiarity of respondents with regulatory requirements and guidelines (Table 12).

Table 12: Knowledge/Experience of regulatory requirements and international guidelines (All respondents)

	No know/exp		Little know/exp		Theoretical know only		Working knowledge		Extensive experience	
Topic	n	%	n	%	n	%	n	%	n	%
ICH E3 – Structure and content of clinical study reports	11	37.9	4	13.8	1	3.4	10	34.5	3	10.3
ICH E6 – Good clinical practice	11	37.9	3	10.3	4	13.8	8	27.6	3	10.3
ICH E9 – Statistical principles for CTs	6	20.7	1	3.4	3	10.3	13	44.8	6	20.7
ICH E10 –Choice of control group in CTs	7	24.1	5	17.2	3	10.3	10	34.5	4	13.8
PSI SOP guidance documents	17	58.6	4	13.8	3	10.3	4	13.8	1	3.4
21 CFR Part 11 – Electronic records and electronic signatures	18	62.1	4	13.8	3	10.3	4	13.8		
Regulatory submission process	18	62.1	7	24.1	3	10.3			1	3.4
Guidelines for Good Practice in the Conduct of CTs in Human Participants in SA	14	48.3	8	27.6	3	10.3	3	10.3	1	3.4
IECs and IRBs	10	34.5	8	27.6	3	10.3	5	17.2	3	10.3

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience'

Know = Knowledge, Exp = Experience, IECs = Independent Ethics Committees, IRBs = Institutional Review Boards, CTs = Clinical trials, SA = South Africa

Approximately half of the respondents have no or little knowledge of the ICH guidelines for the structure and content of clinical study reports and for GCP. This frequency was lower for the guideline on the choice of a control group in clinical trials at about 40% of the respondents. In contrast, only 24.1% of the respondents had little or no knowledge of the ICH guideline on statistical principles for clinical research. For the remainder of the topics over 70% of the respondents had little or no knowledge of the regulation, process or guideline.

CROs had a higher proportion of respondents with at least a theoretical knowledge in all these topics compared to university and government research agencies. This contrast was notable for the four ICH guidelines where nearly all CRO biostatisticians had at least a theoretical knowledge compared to about a quarter of the university and government research agency biostatisticians for ICH E3 and ICH E6 and about half of the university and government research agency biostatisticians for ICH E9 and ICH E10. Even though below 50% of the CRO biostatisticians had at least a theoretical knowledge for the rest of the topics (except for Electronic records and signatures for which 60% had

knowledge) the other subgroups still exhibited lower proportions of respondents with at least theoretical knowledge (Table S.7a, Appendix G).

Table 13: Method of acquiring knowledge/experience regarding regulatory requirements and international guidelines (All respondents)

	University degree		On-the-job training		Formal in-house train.		Self-study/ reading		Other train. course(s)	
Topic	n	%	n	%	n	%	n	%	n	%
ICH1 E3 – Structure and content of clinical study reports	1	3.4	12	41.4	7	24.1	9	31.0	2	6.9
ICH E6 – Good clinical practice	2	6.9	10	34.5	10	34.5	10	34.5	2	6.9
ICH E9 – Statistical principles for CTs	3	10.3	16	55.2	10	34.5	14	48.3	1	3.4
ICH E10 –Choice of control group in CTs	3	10.3	11	37.9	6	20.7	10	34.5	1	3.4
PSI2 SOP3 guidance documents	1	3.4	4	13.8	3	10.3	5	17.2	1	3.4
21 CFR Part 11 – Electronic records and electronic signatures			4	13.8	5	17.2	4	13.8	1	3.4
Regulatory submission process			6	20.7	2	6.9	4	13.8	1	3.4
Guidelines for Good Practice in the Conduct of CTs in Human Participants in SA			5	17.2	4	13.8	7	24.1	3	10.3
IECs and IRBs	1	3.4	12	41.4	3	10.3	6	20.7	3	10.3

Note: Train. = Training, IECs = Independent Ethics Committees, IRBs = Institutional Review Boards, CTs = Clinical trials, SA = South Africa

A respondent could indicate more than one method of acquiring knowledge/experience in a specific topic

Similarly to the previous group of topics it appears that the respondents who indicated that they had at least a little knowledge/experience of a topic, acquired the knowledge through on-the-job training followed by self-study and reading and formal in-house training (Table 13). Very few respondents indicated learning about these topics through other training courses and university degrees.

The methods of acquiring knowledge differed in the subgroups and were similar to those seen in the previous section. Clinical trial biostatisticians working in CROs mostly acquired their knowledge through on-the-job training and formal in-house training and to a lesser extent self-study and reading. University biostatisticians learned through on-the-job training and government research agencies primarily acquired knowledge through self-study and reading (Table S.7b, Appendix G).

3.1.3.3 Clinical trial design

A clinical trial biostatistician provides input into the overall design of a clinical trial. The table below describes the knowledge and experience of respondents in clinical trial design topics (Table 14).

Table 14: Knowledge/Experience of clinical trial design (All respondents)

	No know/exp		Little know/exp		Theoretical know only		Working knowledge		Extensive experience	
Topic	n	%	n	%	n	%	n	%	n	%
Types of clinical trials (superiority, etc.)	4	13.8	4	13.8	3	10.3	15	51.7	3	10.3
Clinical trial designs (parallel, etc)	1	3.4	2	6.9	5	17.2	14	48.3	7	24.1
Types of outcome variables (composite variables, etc)	3	10.3	2	6.9	2	6.9	18	62.1	4	13.8
Sample size calculation	2	6.9	2	6.9	8	27.6	11	37.9	6	20.7
Statistical considerations for protocol review (including protocol amendments)	5	17.2	3	10.3	2	6.9	14	48.3	5	17.2
Randomisation and blinding	3	10.3	3	10.3	7	24.1	10	34.5	6	20.7
Statistical considerations for CRF design	7	24.1	4	13.8	5	17.2	6	20.7	7	24.1
Statistical considerations for interim analyses	5	17.2	5	17.2	5	17.2	10	34.5	4	13.8
Statistical considerations for DSMBs	16	55.2	3	10.3	7	24.1	3	10.3		
Avoiding bias in clinical trials	2	7.1	5	17.9	5	17.9	12	42.9	4	14.3

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience'

Know = Knowledge, Exp = Experience, DSMBs = Data Safety Monitoring Boards

Most of the respondents (>70%) have at least a theoretical knowledge in all except three of these topics. The topics with which the respondents were less familiar were the statistical considerations for CRF design, statistical considerations for interim analyses and statistical considerations for DSMBs.

Nearly all clinical trial biostatisticians working in CROs showed at least a theoretical knowledge in these statistical design topics with the smallest proportion exhibiting knowledge in the statistical considerations for DSMBs. The next subgroup showing the highest proportion of clinical trial biostatisticians knowledgeable in these topics was the biostatisticians employed by government research agencies. The topics with the lowest proportions in government research agencies were statistical considerations for protocol review, CRF design and DSMBs. University biostatisticians were less familiar with the topics

than the other two subgroups with the lowest proportion of biostatisticians being familiar with the statistical considerations for DSMBs, as observed in the other groups (Table S.8a, Appendix G).

Table 15: Method of acquiring knowledge/experience regarding clinical trial design (All respondents)

	University degree		On-the-job training		Formal in-house train.		Self-study/ reading		Other train. course(s)	
Topic	n	%	n	%	n	%	n	%	n	%
Types of clinical trials (superiority, etc.)	5	17.2	18	62.1	8	27.6	13	44.8	1	3.4
Clinical trial designs (parallel, etc)	9	31.0	18	62.1	8	27.6	18	62.1	1	3.4
Types of outcome variables (composite variables, etc)	4	13.8	18	62.1	5	17.2	15	51.7	1	3.4
Sample size calculation	16	55.2	15	51.7	3	10.3	16	55.2	1	3.4
Statistical considerations for protocol review (including protocol amendments)	2	6.9	19	65.5	2	6.9	7	24.1		
Randomisation and blinding	9	31.0	12	41.4	7	24.1	12	41.4	1	3.4
Statistical considerations for CRF design	4	13.8	14	48.3	4	13.8	10	34.5		
Statistical considerations for interim analyses	3	10.3	15	51.7	6	20.7	10	34.5	1	3.4
Statistical considerations for DSMBs	2	6.9	8	27.6	3	10.3	7	24.1	1	3.4
Avoiding bias in clinical trials	10	34.5	17	58.6	8	27.6	14	48.3	1	3.4

Note: Train. = Training, DSMBs = Data Safety Monitoring Boards

A respondent could indicate more than one method of acquiring knowledge/experience in a specific topic

Knowledge and experience in these topics, except for sample size calculation, were mostly acquired through on-the-job training and self-study and reading, followed by formal in-house training (Table 15). Respondents learned about sample size calculation through their university degrees, on-the-job training and self-study and reading.

The methods of acquiring knowledge in each of the subgroups are similar to those seen in the section discussed previously. Clinical trial biostatisticians employed by CROs mostly acquired their knowledge through on-the-job training and formal in-house training and to a lesser extent self-study and reading. University biostatisticians largely learned through on-the-job training and government research agencies acquired knowledge through self-study and reading (Table S.8b, Appendix G).

3.1.3.4 Data management

A clinical trial biostatistician is required to provide input into the data management processes for a clinical trial and the table below presents respondent's knowledge and experience in data management related topics (Table 16).

Table 16: Knowledge/Experience of data management (All respondents)

	No know/exp		Little know/exp		Theoretical know only		Working knowledge		Extensive experience	
Topic	n	%	n	%	n	%	n	%	n	%
Data management for clinical trials	2	6.9	4	13.8	4	13.8	15	51.7	4	13.8
Biostatistical input into data management processes	2	6.9	3	10.3	2	6.9	18	62.1	4	13.8
Conducting the statistical review of a database	6	20.7	4	13.8	3	10.3	10	34.5	6	20.7

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience'

Know = Knowledge, Exp = Experience

Most of the respondents have at least a theoretical understanding of data management for clinical trials and biostatistical input into data management processes. Although about 65% of respondents have more than a theoretical understanding of conducting a statistical review of a database this percentage is lower than was observed for the other topics in this category.

All the subgroups indicated a reasonably high proportion of clinical trial biostatisticians with at least a theoretical knowledge of data management for clinical trials and biostatistical input into data management processes. The proportion of biostatisticians with at least a theoretical knowledge of conducting the statistical review of a database was good in CROs and universities and poor in government research agencies (Table S.9a, Appendix G).

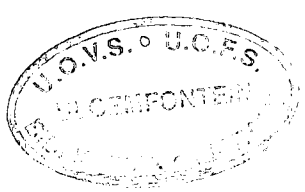


Table 17: Method of acquiring knowledge/experience regarding data management (All respondents)

	University degree		On-the-job training		Formal in-house train.		Self-study/ reading		Other train. course(s)	
Topic	n	%	n	%	n	%	n	%	n	%
Data management for clinical trials	3	10.3	20	69.0	11	37.9	10	34.5		
Biostatistical input into data management processes	2	6.9	21	72.4	8	27.6	11	37.9		
Conducting the statistical review of a database	1	3.4	17	58.6	5	17.2	7	24.1		

Note: Train. = Training

A respondent could indicate more than one method of acquiring knowledge/experience in a specific topic

As with previous groups of topics it appears that the respondents, who did indicate that they at least had a little knowledge/experience of a topic, acquired the knowledge through on-the-job training followed by self-study and reading and formal in-house training (Table 17). Very few respondents indicated learning about these topics through university degrees and none through other training courses.

Clinical trial biostatisticians working in CROs generally acquired their knowledge in these data management topics through on-the-job training followed by formal in-house training. Those biostatisticians employed by universities and government research agencies learned through on-the-job training; with government research agencies also gaining knowledge through self-study and reading (Table Subgroup.9b, Appendix G).

3.1.3.5 Statistical analysis considerations

There are various considerations that a clinical trial biostatistician needs to take into account when analysing a clinical trial. The following table presents the familiarity of respondents with these topics (Table 18).

Table 18: Knowledge/Experience of statistical analysis considerations (All respondents)

	No know/exp		Little know/exp		Theoretical know only		Working knowledge		Extensive experience	
Topic	n	%	n	%	n	%	n	%	n	%
Writing statistical analysis plans	3	10.3	3	10.3	2	6.9	12	41.4	9	31.0
Writing derived dataset specifications	9	31.0	7	24.1	3	10.3	8	27.6	2	6.9
Identifying analysis populations	6	20.7	2	6.9	1	3.4	15	51.7	5	17.2
Conducting a blind review of data	9	31.0	5	17.2			11	37.9	4	13.8
Presentation/analysis of demographic and background data	2	6.9					15	51.7	12	41.4
Presentation/analysis of laboratory data	2	6.9	2	6.9			19	65.5	6	20.7
Presentation/analysis of adverse events	5	17.2	3	10.3			16	55.2	5	17.2
Presentation/analysis of concomitant illnesses and medication, medical history and previous medications	5	17.2	2	6.9			17	58.6	5	17.2
Data analysis considerations (covariates, interactions, etc)	3	10.3			1	3.4	18	62.1	7	24.1
International medical coding dictionaries	10	34.5	5	17.2			13	44.8	1	3.4
Programming considerations and documentation (Good programming practices)	4	13.8	3	10.3			17	58.6	5	17.2
Pharmacokinetics & Pharmacodynamics	10	34.5	2	6.9	5	17.2	9	31.0	3	10.3
Bioequivalence studies	9	31.0	6	20.7	3	10.3	6	20.7	5	17.2

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience'

Know = Knowledge, Exp = Experience

More than 70% of the respondents reported at least a theoretical knowledge in all topics except writing derived dataset specifications, international coding dictionaries, pharmacokinetics and pharmacodynamics, and bioequivalence studies.

Nearly all the CRO respondents have at least a theoretical knowledge in statistical analysis considerations as listed in the questionnaire. The topic with which they were the least familiar was bioequivalence studies (60.0% of the CRO respondents indicated that they had at least a theoretical knowledge). Biostatisticians employed by government research agencies and university biostatisticians had less experience in these statistical analysis consideration topics than was observed for CRO biostatisticians. The topics with which government research agency biostatisticians are most familiar are the presentation and analysis of demographic and background data and other data

analysis considerations such as covariates, interactions etc. For these topics too university biostatisticians indicated that they were most knowledgeable (Table S.10a, Appendix G).

Table 19: Method of acquiring knowledge/experience regarding statistical analysis considerations (All respondents)

	University degree		On-the-job training		Formal in-house train.		Self-study/ reading		Other train. Course(s)	
Topic	n	%	n	%	n	%	n	%	n	%
Writing statistical analysis plans	4	13.8	21	72.4	9	31.0	12	41.4		
Writing derived dataset specifications	1	3.4	13	44.8	4	13.8	4	13.8		
Identifying analysis populations	2	6.9	18	62.1	10	34.5	10	34.5		
Conducting a blind review of data	1	3.4	14	48.3	9	31.0	7	24.1		
Presentation/analysis of demographic and background data	7	24.1	21	72.4	9	31.0	12	41.4		
Presentation/analysis of laboratory data	3	10.3	21	72.4	8	27.6	11	37.9		
Presentation/analysis of adverse events	3	10.3	20	69.0	7	24.1	7	24.1		
Presentation/analysis of concomitant illnesses and medication, medical history and previous medications	2	6.9	19	65.5	7	24.1	8	27.6		
Data analysis considerations (covariates, interactions, etc)	11	37.9	19	65.5	4	13.8	12	41.4		
International medical coding dictionaries	1	3.4	14	48.3	9	31.0	7	24.1		
Programming considerations and documentation (Good programming practices)	3	10.3	19	65.5	9	31.0	10	34.5		
Pharmacokinetics & Pharmacodynamics	4	13.8	10	34.5	9	31.0	9	31.0		
Bioequivalence studies	5	17.2	9	31.0	7	24.1	10	34.5		

Note: Train. = Training

A respondent could indicate more than one method of acquiring knowledge/experience in a specific topic

Knowledge in these topics was mostly acquired through on-the-job training (Table 19). Self-study and reading were the next most frequently used methods of knowledge acquisition followed very closely by formal in-house training. Eleven of the respondents (37.9%) indicated that they learned of data analysis considerations such as covariates and interactions through their university degree.

On-the-job training followed by formal in-house training were the most frequent methods of knowledge acquisition for CRO clinical trial biostatisticians. On-the-job training was mostly used to develop university biostatisticians in these topics

and a mixture of on-the-job training, self-study and reading was used to train biostatisticians employed by government research agencies (Table S.10b, Appendix G).

3.1.3.6 Statistical methods

The knowledge and experience of respondents in the statistical methods most commonly used in the analysis of clinical trials are summarised in the table below (Table 20).

Table 20: Knowledge/Experience of statistical methods (All respondents)

	No know/exp		Little know/exp		Theoretical know only		Working knowledge		Extensive experience	
Topic	n	%	n	%	n	%	n	%	n	%
ANOVA/ANCOVA			1	3.4	2	6.9	10	34.5	16	55.2
Linear regression	1	3.4	1	3.4	4	13.8	11	37.9	12	41.4
Repeated measures/Multivariate analysis	1	3.4			5	17.2	12	41.4	11	37.9
Non-parametric methods	1	3.4			3	10.3	14	48.3	11	37.9
Contingency tables	1	3.4			2	6.9	11	37.9	15	51.7
Risk ratios / odds ratios / Mantel-Haenzel method	1	3.4	1	3.4	4	13.8	12	41.4	11	37.9
Logistic regression	2	6.9	2	6.9	4	13.8	12	41.4	9	31.0
Generalised linear models	1	3.4	1	3.4	3	10.3	13	44.8	11	37.9
Exact tests			2	6.9	3	10.3	12	41.4	12	41.4
Analysis of survival data (incl. Cox regression, Kaplan-Meier estimates)	3	10.3	3	10.3	3	10.3	12	41.4	8	27.6

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience'

Know = Knowledge, Exp = Experience

Very few of the respondents indicated that they did not have at least a theoretical knowledge in these statistical methods, with the majority having either a working knowledge or extensive experience (Table 20). The same results were observed in the subgroup analyses (Table S.11a, Appendix G).

Table 21: Method of acquiring knowledge/experience regarding statistical methods (All respondents)

	University degree		On-the-job training		Formal in-house train.		Self-study/ reading		Other train. Course(s)	
Topic	n	%	n	%	n	%	n	%	n	%
ANOVA/ANCOVA	26	89.7	19	65.5	3	10.3	14	48.3	1	3.4
Linear regression	24	82.8	15	51.7	2	6.9	13	44.8	1	3.4
Repeated measures/Multivariate analysis	20	69.0	17	58.6	2	6.9	14	48.3	2	6.9
Non-parametric methods	22	75.9	19	65.5	1	3.4	15	51.7		
Contingency tables	23	79.3	21	72.4	3	10.3	14	48.3	1	3.4
Risk ratios / odds ratios / Mantel-Haenzel method	16	55.2	19	65.5	1	3.4	14	48.3	2	6.9
Logistic regression	14	48.3	15	51.7	2	6.9	14	48.3	3	10.3
Generalised linear models	19	65.5	18	62.1	2	6.9	14	48.3	1	3.4
Exact tests	18	62.1	20	69.0	2	6.9	13	44.8		
Analysis of survival data (incl. Cox regression, Kaplan-Meier estimates)	9	31.0	17	58.6	2	6.9	15	51.7	2	6.9

Note: Train. = Training

A respondent could indicate more than one method of acquiring knowledge/experience in a specific topic

The respondents mostly acquired their knowledge though a university degree (Table 21). Many of the respondents also learned about these statistical methods through on-the-job training and self-study and reading.

Table S.11b (Appendix G) confirms that clinical trial biostatisticians, regardless of their industry of employment, learned of these statistical methods primarily through their university education followed by on-the-job training. Biostatisticians employed by government research agencies tended towards reporting learning by self-study and reading a little more frequently than in the other two subgroups.

3.1.3.7 Reporting

Once the analysis results have been presented in tables, listings and graphs the clinical trial biostatistician is required to write or at least contribute to the clinical trial report. The following table describes the knowledge and experience of respondents in medical writing and reporting topics (Table 22).

Table 22: Knowledge/Experience of reporting (All respondents)

Topic	No know/exp		Little know/exp		Theoretical know only		Working knowledge		Extensive experience	
	n	%	n	%	n	%	n	%	n	%
Medical writing (scientific writing) style and conventions	3	10.3	7	24.1			11	37.9	8	27.6
Writing/reviewing publications	5	17.2	6	20.7	1	3.4	10	34.5	7	24.1
Writing/reviewing clinical study report	4	13.8	6	20.7			13	44.8	6	20.7

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience'

Know = Knowledge, Exp = Experience

Approximately 65% of the respondents had either a working knowledge or extensive experience in medical writing style and conventions, writing/reviewing publications and writing/reviewing clinical study reports. The rest of the respondents had either no, or little, knowledge or experience in these topics, except for one respondent who indicated a theoretical knowledge in writing/reviewing publications.

Clinical trial biostatisticians employed by government research agencies are most familiar with medical writing conventions and the writing and reviewing of publications and CRO biostatisticians are most familiar with writing and reviewing clinical study reports (Table S.12a, Appendix G).

Table 23: Method of acquiring knowledge/experience regarding reporting (All respondents)

Topic	University degree		On-the-job training		Formal in-house train.		Self-study/ reading		Other train. Course(s)	
	n	%	n	%	n	%	n	%	n	%
Medical writing (scientific writing) style and conventions	2	6.9	20	69.0	6	20.7	9	31.0		
Writing/reviewing publications	3	10.3	16	55.2	4	13.8	10	34.5		
Writing/reviewing clinical study report	2	6.9	19	65.5	9	31.0	8	27.6	1	3.4

Note: Train. = Training

The knowledge and experience mentioned above was mostly acquired through on-the-job training, self-study and reading (Table 23). Some respondents also acquired knowledge through formal in-house training.

On-the-job training featured as the leading method of acquiring knowledge in biostatisticians employed by CROs and universities and as a secondary method in biostatisticians employed by government research agencies. Formal in-house training was also used to train CRO biostatisticians in writing and reviewing clinical study reports. The primary method for becoming familiar with reporting topics for government research agency biostatisticians was self-study and reading (Table S.12b, Appendix G).

3.1.3.8 Quality control and documentation

Quality control and review procedures need to be implemented by the clinical trial biostatistician to ensure accurate representation of the data and results. The table below summarises the knowledge and experience respondents in quality control and documentation topics (Table 24).

Table 24: Knowledge/Experience of quality control and documentation (All respondents)

	No know/exp		Little know/exp		Theoretical know only		Working knowledge		Extensive experience	
Topic	n	%	n	%	n	%	n	%	n	%
Quality control and review processes	7	24.1	4	13.8	3	10.3	12	41.4	3	10.3
Maintaining project documentation (including version control etc)	6	20.7	6	20.7	2	6.9	12	41.4	3	10.3
Paper and electronic archiving	7	24.1	5	17.2	1	3.4	15	51.7	1	3.4

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience'

Know = Knowledge, Exp = Experience

At least a theoretical knowledge in quality control and documentation topics was reported by about 60% of the respondents. Thus 40% of respondents are not familiar with the quality control and review process, maintaining project documentation and archiving.

The majority of clinical trial biostatisticians employed by CROs are knowledgeable in all three quality control and documentation topics. Biostatisticians employed by universities and government research agencies recorded that they are not as familiar with these topics. This contrast resulted in the lowering of the overall percentage to 60.0% of clinical trial biostatisticians

having at least a theoretical knowledge in these topics (Table S.13a, Appendix G).

Table 25: Method of acquiring knowledge/experience regarding quality control and documentation (All respondents)

	University degree		On-the-job training		Formal in-house train.		Self-study/ reading		Other train. course(s)	
Topic	n	%	n	%	n	%	n	%	n	%
Quality control and review processes	3	10.3	14	48.3	4	13.8	6	20.7		
Maintaining project documentation (including version control etc)	2	6.9	17	58.6	4	13.8	5	17.2		
Paper and electronic archiving	1	3.4	18	62.1	4	13.8	4	13.8		

Note: Train. = Training

A respondent could indicate more than one method of acquiring knowledge/experience in a specific topic

The majority of the respondents acquired their knowledge and experience through on-the-job training (Table 25). This method was the primary training in all three subgroups. In additional formal in-house training was also used to teach clinical trial biostatisticians employed by CROs (Table S.13b, Appendix G).

3.1.3.9 Computer skills/packages

The following table presents the knowledge and experience of respondents regarding computer skills and packages (Table 26).

Table 26: Knowledge/Experience of computer skill and packages (All respondents)

	No know/exp		Little know/exp		Theoretical know only		Working knowledge		Extensive experience	
Topic	n	%	n	%	n	%	n	%	n	%
MS Word							12	41.4	17	58.6
MS Excel							14	48.3	15	51.7
MS PowerPoint	1	3.4	3	10.3			17	58.6	8	27.6
Nquery	20	69.0	4	13.8	2	6.9	2	6.9	1	3.4
StatXact	20	69.0	3	10.3	1	3.4	3	10.3	2	6.9
WinNonLin	25	86.2	1	3.4	1	3.4	1	3.4	1	3.4
SAS			1	3.4			14	48.3	14	48.3
CIA	21	72.4	2	6.9			4	13.8	2	6.9

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience'

Know = Knowledge, Exp = Experience

All of the respondents had a working knowledge or extensive experience in working with Microsoft Word and Excel, and all but one in working with SAS®. Very few respondents were familiar with Nquery®, StatXact®, WinNonLin® and CIA®. Most of the respondents have at least a working knowledge of Microsoft PowerPoint.

The knowledge and experience of clinical trial biostatisticians in the computer skills and packages listed in the questionnaire does not differ much between the industry subgroups (Table S.14a, Appendix G).

Table 27: Method of acquiring knowledge/experience regarding computer skills and packages (All respondents)

	University degree		On-the-job training		Formal in-house train.		Self-study/ reading		Other train. course(s)	
Topic	n	%	n	%	n	%	n	%	n	%
MS Word	10	34.5	18	62.1	5	17.2	19	65.5	2	6.9
MS Excel	9	31.0	17	58.6	3	10.3	19	65.5	1	3.4
MS PowerPoint	3	10.3	13	44.8	1	3.4	16	55.2	2	6.9
Nquery			3	10.3	2	6.9	4	13.8		
StatXact	2	6.9	3	10.3	2	6.9	3	10.3		
WinNonLin			1	3.4			2	6.9		
SAS	7	24.1	23	79.3	11	37.9	19	65.5	3	10.3
CIA			4	13.8			5	17.2		

Note: Train. = Training.

A respondent could indicate more than one method of acquiring knowledge/experience in a specific topic

Respondents mostly became familiar with SAS® through on-the-job training and self-study and reading (Table 27). Some of the respondents have attended formal in-house training in SAS® and a quarter of the respondents had learned of SAS® during their university degree. Microsoft Word and Excel were mostly learned through self-study and reading (65.5% of respondents), followed closely by on-the-job training. Above 30% of respondents were taught about Word and Excel during their university degree. Respondents became familiar with PowerPoint through self-study and reading followed by on-the-job training. As seen above, very few respondents have acquired knowledge and experience in Nquery, StatXact, WinNonLin and CIA.

CRO clinical trial biostatisticians became familiar with these computer packages mostly through on-the-job training and self-study and reading. These biostatisticians also received formal in-house training for SAS® and learned about Microsoft Word and Excel during their university studies. Self-study and reading were most often used to learn about these computer packages by biostatisticians employed in universities and government research agencies. On-the-job training was the second most frequently reported method of teaching computer skill and packages in universities and government research agencies (Table S.14b, Appendix G).

3.1.3.10 Other appropriate topics

The list below contains the topics listed under "other appropriate topics" by respondents on their questionnaires (Table 28). All of the topics were only mentioned once except for epidemiology, which was mentioned twice. Where possible, each of the topics has been assigned to the appropriate section as defined in the clinical trial biostatistician questionnaire.

Table 28: List of other appropriate topics (All respondents)

Other appropriate topic	Questionnaire section
ClinTrial: Design of a database	Computer skills/packages
Fortran	Computer skills/packages
Other sample size calculation software (Epi Info 2000, PS Power and Sample Size Calculation)	Computer skills/packages
Other BE software (HOEREP, in-house designed Software)	Computer skills/packages
Programming language: C++ Builder	Computer skills/packages
Programming language: Matlab	Computer skills/packages
SYSTAT	Computer skills/packages
SPSS	Computer skills/packages
Cluster randomised clinical trials	Clinical trial design
Meta-analysis of randomised clinical trials	Clinical trial design
Pragmatic randomised clinical trials	Clinical trial design
Epidemiology	Clinical trial design
Minimisation	Statistical methods
Bayesian analysis	Statistical methods
Cochrane collaboration	-
Systems	-
Design and maintenance of quality assessment database	-
International Standards Organisation (ISO 9001-2000)	-
Consent statement	Clinical trial design and regulatory requirements and international guidelines

3.2 UNIVERSITY COURSE CONTENT SURVEY

3.2.1 Response rates

Twenty South African universities were approached to provide information regarding the statistics courses they presented. Information was obtained for fourteen (70.0%) of these universities. There was no response from six of the universities.

3.2.2 Number of undergraduate university statistics courses

In South Africa an undergraduate degree, a bachelors degree, equates to three-years of full-time study. Thereafter a student may complete a fourth year known as an Honours degree. A university course is defined differently at the various South African universities. Courses range from three-month courses to full-year courses, but all courses are restricted to a specific year of study. Courses were counted as defined by each university and not normalised to be courses of equivalent length.

Table 29: Number of first-, second- and third-year statistics courses presented at South African universities

		n	%
Number of first-year courses	<= 3 courses	4	28.6
	4 - 7 courses	7	50.0
	8 - 11 courses	3	21.4
	Total	14	100.0
Number of second-year courses	<= 3 courses	4	28.6
	4 - 7 courses	8	57.1
	8 - 11 courses	2	14.3
	Total	14	100.0
Number of third-year courses	<= 3 courses	3	21.4
	4 - 7 courses	6	42.9
	8 - 11 courses	2	14.3
	12 - 15 courses	2	14.3
	> = 16 courses	1	7.1
	Total	14	100.0

Note: A university course may differ in length, varying from a three month course to a twelve month course

Approximately half of the responding universities presented between four and seven first-, second- and third-year courses (Table 29).

3.2.3 Content of undergraduate university statistics courses

The table below summarises the number of South African universities that have at least one course (first-, second- or third-year course) addressing the topics identified on the clinical trial biostatistician questionnaire (Table 30).

Table 30: South African universities with at least one course addressing a specific questionnaire topic (topics as identified on the clinical trial biostatistician questionnaire)

		First-year course		Second-year course		Third-year course		Any year	
Section	Topic	n	%	n	%	N	%	n	%
Clinical trial Design	Clinical trial designs	1	7.1	0	0.0	0	0.0	1	7.1
	Sample size calculation	2	14.3	1	7.1	0	0.0	3	21.4
	Randomisation and blinding	0	0.0	2	14.3	0	0.0	2	14.3
Computer skills/packages	MS Word	1	7.1	0	0.0	0	0.0	1	7.1
	MS Excel	2	14.3	2	14.3	1	7.1	4	28.6
	SAS	1	7.1	1	7.1	0	0.0	2	14.3
	Computer usage: package not specified	6	42.9	6	42.9	5	35.7	10	71.4
	Computer usage: package specified but not in questionnaire	3	21.4	0	0.0	3	21.4	5	35.7
Other	Project	1	7.1	2	14.3	3	21.4	5	35.7
Quality control and documentation	Quality control and review processes	1	7.1	0	0.0	4	28.6	5	35.7
Statistical methods	Analysis of continuous data	14	100.0	11	78.6	6	42.9	14	100.0
	ANOVA/ANCOVA	11	78.6	8	57.1	9	64.3	13	92.9
	Linear regression	13	92.9	9	64.3	8	57.1	13	92.9
	Repeated measures/Multivariate analysis	1	7.1	6	42.9	6	42.9	10	71.4
	Non-parametric methods	9	64.3	3	21.4	5	35.7	12	85.7
	Analysis of binary and categorical data	14	100.0	9	64.3	3	21.4	14	100.0
	Contingency tables	7	50.0	3	21.4	2	14.3	9	64.3
	Risk ratios / odds ratios / Mantel-Haenzel method	1	7.1	0	0.0	1	7.1	2	14.3
	Logistic regression	1	7.1	3	21.4	7	50.0	8	57.1
	Generalised linear models	0	0.0	0	0.0	10	71.4	10	71.4
	Exact tests	0	0.0	0	0.0	0	0.0	0	0.0
	Analysis of survival data (incl. Cox regression, Kaplan-Meier estimates)	1	7.1	0	0.0	5	35.7	5	35.7

Note: A university course may differ in length, varying from a three month course to a twelve month course

Very few South African universities presented courses covering topics outside of the Statistical Methods Section as identified on the clinical trial biostatistician questionnaire. The most frequently covered courses other than those under statistical methods were:

- courses identified as having a computer usage component (mostly the computer package used was not identified),
- courses covering quality control (4 universities covered third-year courses in this topic), and
- projects which require students to collect, analyse and report data.

Statistical methods topics that are well covered by courses from first-year through to third-year are:

- Analysis of continuous data (which includes the comparison of continuous data, p-values, point estimates and confidence intervals),
- ANOVA/ANCOVA,
- Linear regression,
- Analysis of binary and categorical data (which includes the comparison of binary and categorical data, p-values, point estimates and confidence intervals),
- Generalised linear models (at a third-year course level),
- Non-parametric methods (to a lesser degree than the previous courses, but still reasonably well covered).

Statistical methods topics that are included in courses from about half of the South African universities that responded to the request for information are:

- Repeated measures/multivariate analysis,
- Contingency tables,
- Logistic regression.

Analysis of survival data including Cox regression and Kaplan-Meier estimates was included in 35.7% of the third-year courses at the South African universities.

Statistical methods topics as identified on the clinical trial biostatistician questionnaire which are not well covered by courses presented by South African universities are exact tests, risk ratios, odds ratios and Mantel-Haenzel methods.

The table below summarises the number of first-, second- or third-year courses presented at South African universities addressing the topics as identified on the clinical trial biostatistician questionnaire (Table 31).

Table 31: Number of courses presented by South African universities covering a specific questionnaire topic - Topics as identified on the clinical trial biostatistician questionnaire

Section	Topic	First-year course	Second-year Course	Third-year course
Clinical trial design	Clinical trial designs	1		
	Sample size calculation	3	1	
	Randomisation and blinding		2	
Computer skills/packages	MS Word	1		
	MS Excel	3	5	1
	SAS	1	1	
	Computer usage: package not specified	14	16	16
	Computer usage: package specified but not in questionnaire list	3		4
Other	Project	1	2	3
Quality control and documentation	Quality control and review processes	1		6
Statistical methods	Analysis of continuous data	37	17	11
	ANOVA/ANCOVA	18	12	18
	Linear regression	28	14	13
	Repeated measures/Multivariate analysis	1	7	11
	Non-parametric methods	11	4	5
	Analysis of binary and categorical data	31	14	6
	Contingency tables	11	3	2
	Risk ratios / odds ratios / Mantel-Haenzel method	1		1
	Logistic regression	2	3	10
	Generalised linear models			16
	Exact tests			
	Analysis of survival data (incl. Cox regression, Kaplan-Meier estimates)	1		6

Note: A university course may differ in length, varying from a three month course to a twelve month course

The most frequently presented topics are similar to those identified as most frequent in the analysis of the number of universities presenting at least one

course in a specific topic. This similarity was also observed for the topics which are well covered by courses from first-year through to third-year and for the topics which were seldomly included in courses.

CHAPTER 4: DISCUSSION

4.1 SURVEY OF PROFILE OF CLINICAL TRIAL BIOSTATISTICIANS

4.1.1 Response rates

The response rate of institutions contacted to provide names and contact details for clinical trial biostatisticians was generally high. The response was also high for contacts who received their questionnaires, whether with a response that they had been incorrectly identified as a clinical trial biostatistician or a completed questionnaire.

Individuals on the SASA consultants list were contacted as a last resort in an effort to include clinical trial biostatisticians working privately in the survey. The high level of delivery failures when sending questionnaires was attributed to the SASA consultants list being out-of-date. An effort was made to find alternative contact details for these delivery failures but success was only achieved for three respondents.

Aside from the SASA consultants list it appears that the sampling frame reasonably accurately represented the population being assessed. Many of the respondents working for government agencies who indicated that they did not practice as clinical trial biostatisticians stated that they worked as biostatisticians but were not exposed to clinical trials.

The respondents represent the population of South African clinical trial biostatisticians reasonably well with the exception of the statisticians employed by CROs. Since one of the two CRO's that employ a relatively large number of biostatisticians refused to participate in the survey, most of the respondents from CROs originate from one company.

4.1.2 Profile of clinical trial biostatisticians

Data on the education and training, experience (including years of experience, types of tasks performed, phase of clinical trials analysed, etc) and industry of employment was collected in the clinical trial biostatistician questionnaire in

order to describe the profile of clinical trial biostatisticians employed in South Africa.

4.1.2.1 Qualifications

The minimum industry qualification requirement for clinical trial biostatisticians in Europe (EFSPI Working Group, 1999) is at least a three-year degree in statistics or an equivalent qualification. All the respondents complied with this requirement having at least a bachelors degree in statistics, with the majority (89.7%) having in fact a post-graduate degree. More than half of the respondents have at least a masters degree in statistics implying that in respect of qualifications, these respondents qualify to act as senior or principal statisticians as defined by Phillips (1999).

Clinical trial biostatisticians employed by CROs mostly have honours degrees as their highest statistics qualification with one respondent each having a bachelors degree, masters degree and PhD. In both university departments and government research agencies the respondents nearly all have either a masters degree or PhD as their highest statistics qualification.

The statistics qualifications for European clinical trial biostatisticians differ per country ranging between a three-year university degree and a PhD, however most have a masters degree (EFSPI Working Group, 1999).

4.1.2.2 Industry

According to the EFSPI Working Group (1999) most European clinical trial biostatisticians are employed by pharmaceutical companies followed by CROs. A few European clinical trial biostatisticians are employed by universities with a small number being employed by regulatory authorities, although this has increased in recent years.

The type of industry in which clinical trial biostatisticians are employed in South Africa differs from the profile seen in Europe. Since pharmaceutical companies do not have research offices performing statistical analyses in South Africa they are not a potential employer of clinical trial biostatisticians. CROs seem to

employ most of the clinical trial biostatisticians. However, the actual number cannot be quantified because the CRO that refused to participate in the survey employs a relatively large number of biostatisticians.

Information was also collected regarding the industries in which respondents were previously employed. Respondents who answered this question mostly indicated that they were previously employed in the same industry in which they are currently employed. However, it is possible that respondents may have interpreted the question to imply that they should also indicate the industry in which they are currently employed.

4.1.2.3 Experience

4.1.2.3.1 Years of experience

The criteria defined by Phillips (1999) to indicate the acceptable levels of responsibility for clinical trial biostatisticians included the years of relevant experience. A principal statistician should have more than ten years of relevant experience and a senior statistician should have more than five years of relevant experience.

The years of experience in the industry (in medical statistics) reported by the EFSPI Working Group (1999) was limited to four countries: Belgium, Denmark, The Netherlands and Switzerland. The latter three countries reported that the majority of biostatisticians had between one and five or six years of experience. In Belgium the vast majority of biostatisticians are employed by pharmaceutical companies and half of these have over five years of experience.

Over half of the respondents have less than five years of experience and this fact may be indicative of the recent growth of this industry in South Africa and the increased acknowledgement of the necessity for biostatistical input into clinical trials. This lack of experience was observed in all three subgroups. Half of the respondents would be able to act as either senior or principal statisticians based on their level of experience. Although this proportion appears comparable to those countries mentioned previously, except for Belgium, the

European figures relate to 1999 and given the passage of time since publication these figures may be out-of-date.

4.1.2.3.2 Percentage of time as a clinical trial biostatistician

Respondents employed by CROs spend a higher percentage of their time working as clinical trial biostatisticians (as defined for the purpose of the survey) than those employed in government agencies and university departments. The difference observed in the percentage of time spent as a clinical trial biostatistician is as expected because in CROs a biostatistician's primary line of business is being involved in the design, analysis and reporting of clinical trials. In contrast, university biostatisticians are potentially involved in a range of research being performed at a university and clinical trials usually form a small part of the research being performed at these institutions. Biostatisticians working for government agencies are involved in a small number of clinical trials with most of their time being used for epidemiological studies.

4.1.2.3.3 Number of trials analysed in a year

The majority of the respondents analyse up to 6 trials in a year. Clinical trial biostatisticians employed by university departments typically analysed fewer than three clinical trials a year. Those clinical trial biostatisticians employed by CROs analysed between four and six trials a year. Government research agency biostatisticians seemed to have a reasonable spread in the number of trials analysed in a year with a third analysing less than three a year. The number of trials analysed in a year is reasonably well related to the percentage of time spent working as a clinical trial biostatistician.

This profile of number of trials analysed in a year is as expected given that many of the clinical trial biostatisticians employed by universities are involved in research other than clinical trials. Also the government research agency clinical trial biostatisticians are typically involved in more epidemiological work. CRO clinical trial biostatisticians are specifically appointed to analyse clinical trials and therefore they analyse a higher number of trials in a year. This contrast

may possibly imply that CRO clinical trial biostatisticians are likely to have a wider exposure to clinical trials.

4.1.2.3.4 Experience per clinical trial phase

Clinical trial biostatisticians may have experience in analysing clinical trials in different phases of drug development. Clinical trials conducted during the different phases of development often have different design and analysis requirements. It is preferable that statisticians with experience in a particular phase of the development process should be involved in the design and analysis of trials in that development phase.

The phase of development in which clinical trial biostatisticians had most experience differed according to their current industry of employment. CRO biostatisticians generally had experience in Phase III trials, university biostatisticians in Phase I trials and Government research agency biostatisticians in Phase II clinical trials. Although each industry showed a peak of experience in these specific phases, the other phases were reasonably well represented. About half the respondents have experience in each of the development phases, except that university biostatisticians have very little experience in Phase IV trials and government research agency biostatisticians normally do not work on Phase I trials.

It would be advisable that prior to becoming involved in studies in phases of development with which the clinical trial biostatistician is not familiar, the clinical trial biostatistician should learn about issues specific to that phase.

4.1.2.3.5 Task experience

Biostatistical input into clinical trials is required in study design (including protocol writing, CRF design and randomisation), regulatory submission, the clinical conduct of the study, data management and statistical analysis, and in reporting the study results. (Pocock, 1995; Cook, 1995; Lewis et al, 1995 and Köpcke et al, 1998)

Only one respondent had experience in writing clinical development plans which is a task often performed by a principal statistician (Phillips, 1999). Mostly the principal statistician involved in such a task is employed by a pharmaceutical company. The lack of experience reported in this task is understood in the context of none of the pharmaceutical companies in South Africa employing clinical trial biostatisticians.

Approximately half of the respondents had experience in most of the tasks involved in clinical trial design. The planning of clinical trials is mostly restricted to senior clinical trial biostatisticians (Phillips, 1999).

All clinical trial biostatisticians should at least have a level of responsibility comprising the statistical analysis of a clinical trial and the co-authorship of clinical trial reports (Phillips, 1999 and Cook, 1995). All but one of the respondents indicated that they had experience in the statistical analysis of clinical trials. Experience in the writing of clinical trial reports was noted by just over two-thirds of the respondents.

Fewer respondents based at university departments had experience in writing clinical trial reports than at CROs or government research agencies. Clinical trial biostatisticians employed by CROs had less experience in sample size calculation but more experience in the preparation or review of data management plans than respondents in university departments or government research agencies.

4.1.2.4 Summary of the profile of respondents

Table 32 summarises the profile of clinical trial biostatisticians in Europe (EFSPI Working Group, 1999) and includes the profile of respondents for comparison.

Table 32: Profile of clinical trial biostatisticians in Europe

	Employers	Experience	Qualifications	Regulatory	Responsibilities
Belgium	10 Pharma companies employ 65 clinical trial biostatisticians. CROs employ 10 CTBs	Half pharma CTBs have > 5 years, 10% pharma CTBs have > 10 years	Vast majority MSc, one of 6 has a PhD	Regulatory authority does not employ statisticians	Trial design, analysis and reporting, presentations and publications. Senior clinical trial biostatistician signs the protocol and report
Denmark	8 Pharma companies employ 50 clinical trial biostatisticians. CROs employ <10 clinical trial biostatisticians	Range: 0 to 30 years. Majority have 1-6 years	Vast majority MSc, some PhDs, no BScs	Regulatory authority does not employ statisticians	One of the protocol authors – sometimes signs protocol. CTB normally among report authors, reports approved by senior CTB.
France	150 CTBs in 32 pharma companies. 15 CROs employing clinical trial biostatisticians.	-	Originally doctors with statistics training. Now specific statistics training, 4 to 5 years	Regulatory authority does not employ statisticians	-
Germany	Over 100 CTBs in pharma companies, >70 in CROs	-	At least a 4-year degree, usual 6 years. PhD not necessarily required.	The drug regulatory authority employs 2 statisticians	Trial design and planning, data management, anlysis and reporting. Signs protocol and report. Sometimes responsible for Marketing Authorisation Application
	Note: Germany have a certification program, "Certified Medical Biometrician".				
Italy	Pharma companies employ 70 clinical trial biostatisticians. Small number employed by CROs.	-	University degree in statistics or biology. Degree normally 4 or 5 years. Very few CTBs have the equivalent of a PhD.	Regulatory authority does not employ statisticians	Planning Phase, protocol contribution, statistical analysis, writing reports. Head of statistics usually signs the protocol and the report.
The Netherlands	Pharma companies employ 30-35 CTBs CROs and universities employ 10-20 CTBs	Most have 1 to 5 years experience. Minority have >10 years.	MSc is the typical qualification. About 10% of CTBs have a PhD.	Regulatory authority employs an epidemiologist and a part-time statistical consultant	-
	Note: Preparations are underway to establish a scheme for the registration of biostatisticians in the Netherlands				

Table 32: Profile of clinical trial biostatisticians in Europe (cont.)

	Employers	Experience	Qualifications	Regulatory	Responsibilities
Spain	20 CTBs employed by 16 pharma companies, 21 employed by 10 CROs.	-	No typical qualification – negative correlation between statistical qualification and experience.	Regulatory authority does not employ statisticians	-
	Note: Accrediation exists for individuals in Spain with a university degree including at least one year of statistics plus five years experience in applied statistics, two of which should be in medical statistics.				
Sweden	2 large pharma companies emply 70 CTBs Companies use CRO or university statisticians for advice.	-	20 pharma CTBs have a PhD, majority have a BSc or MSc.	The swedish regulatory authority employs three statisticians.	Initially involved in analysis and reporting. More experienced clinical trial biostatisticians have responsibility for protocols, development plans, regulatory contact, publications, etc.
Switzerland	Six pharma companies employ 100 CTBs CROs employ 12 CTBs	Experience ranges from 0 to >20 years, 50% have 1 – 6 years.	60% have an MSc, 40% have a PhD.	Regulatory authority does not employ statisticians	Planning and design, statistical analysis, interpretation and reporting. Statistician is a coauthor and signatory of the protocol and report.
The United Kingdom	Pharma companies employ >400 clinical trial biostatisticians, and CROs >200 CTBs	-	Normally have a degree, with more companies requiring an MSc.	The UK regulatory authority employs three statisticians.	-
	Note: In the United Kingdom after about 5 years of experience (when CTBs can apply for the status of Chartered Statistician of the RSS), they will expect a promotion to senior statistician. While not an accreditation scheme, ordinary membership of PSI is specific to the pharmaceutical industry.				
South Africa	***10 CTBs are employed by CROs, 9 by universities and 8 by government research agencies***	***Half have <5 years experience and about 30% >10 years experience***	***Most CTBs have a bachelors or honours degree. About 35% have an MSc and almost 30% have PhDs***	***The regulatory authority does not employ any statisticians.***	***Involved in design, planning, analysis, reporting, data management, randomisation etc.***

Ref: EFSPI Working Group, 1999, CTB = clinical trial biostatistician, pharma = pharmaceutical

4.1.3 Knowledge of clinical trial biostatisticians

The clinical trial biostatistician questionnaire was designed to assess, amongst other things, the knowledge of respondents in the topics required of an appropriately educated and trained clinical trial biostatistician and to collect information on how they acquired this knowledge (university degree, on-the-job training, formal in-house training, self-study/reading). The topics identified in the questionnaire were grouped into appropriate sections; the results observed for each of these sections are discussed separately below.

4.1.3.1 The drug development process and clinical trials

Clinical trial biostatisticians require a background to clinical trials, the drug development process and the team involved in conducting clinical trials (Chuang-Stein, 1996 and Liss, 2003). The level of knowledge and experience of respondents in the history and rationale of randomised clinical trials and the conduct of a clinical trial is good.

The knowledge of respondents regarding the clinical trial team is not as high as would be preferred. This deficit should, however, only influence the effective communication of the clinical trial biostatistician with the respective members of the team. About half of the respondents have little or no knowledge of the drug development process. This fact is of concern as in order to effectively consult in the design, perform the analysis and report a clinical trial, it would be recommended that the clinical trial biostatistician understands the entire process of drug development and where a specific clinical trial fits into this process.

More CRO biostatisticians had at least a theoretical knowledge of the drug development and clinical trial topics included in the questionnaire compared to university and government research agency biostatisticians. This contrast was especially noteworthy in the 'drug development process' and the 'clinical trial team' where nearly all CRO biostatisticians were knowledgeable compared to less than half of the university biostatisticians and about half of the government research agency biostatisticians.

Knowledge of the drug development process and clinical trials was typically acquired through on-the-job training, followed by self-study and reading and then formal in-house training. Only one respondent became familiar with these topics through an external training course. Formal in-house training affords the opportunity for control regarding content and correct presentation. However, the quality and content of on-the-job training is dependent on the person presenting the training. Self-study and reading are not subject to an external person but they are dependent on the choice of reading materials or the understanding thereof.

The methods of acquiring knowledge differed in the subgroups. Clinical trial biostatisticians working in CROs mostly acquired their knowledge through on-the-job training and formal in-house training and to a lesser extent self-study and reading. University biostatisticians learned through on-the-job training and those in government research agencies primarily learned through self-study and reading followed by on-the-job training.

4.1.3.2 Regulatory requirements and international guidelines

The results of clinical trials are submitted to regulatory authorities in order to obtain registration for the investigational product in the relevant country or countries. Over the years these regulatory authorities have stipulated requirements for the design, conduct, analysis and reporting of these trials. In addition, through an attempt to standardise these requirements and practices in the industry, various guideline documents have been developed (Lewis et al, 1995 and Phillips et al, 2000). Clinical trial biostatisticians should be familiar with these requirements and guidelines.

The lack of knowledge in most of these topics is of concern as these topics ensure that trials are designed, conducted, analysed and reported according to internationally accepted regulatory requirements. Lack of knowledge of these requirements and guidelines may result in the results of a clinical trial not being accepted by a regulatory authority to the subsequent loss of the sponsor company. This loss may exhibit in many ways, including financial losses and

the loss of time since the sponsor company would be required to conduct additional clinical trials.

CROs had a higher proportion of clinical trial biostatisticians with at least a theoretical knowledge of all these topics compared to university and government research agencies. This difference was considerable for the four ICH guidelines included in the questionnaire. Nearly all CRO biostatisticians had at least a theoretical knowledge compared to about a quarter of the university and government research agency biostatisticians for the ICH E3 guideline (1995) and the ICH E6 guideline (1996b), and about half of the university and government research agency biostatisticians for the ICH E9 (1998b) and ICH E10 (2000). Even though less than half of the CRO biostatisticians had at least a theoretical knowledge for the rest of the topics (except for Electronic records and signatures for which 60.0% had knowledge) the other subgroups still reported lower proportions of respondents with at least a theoretical knowledge.

Similarly to the previous group of topics it appears that the respondents, who indicated that they at least had a little knowledge/experience of a topic, acquired the knowledge through on-the-job training followed by self-study and reading and formal in-house training. Very few respondents indicated learning about these topics through other training courses and university degrees. Concerns regarding the content of training and effective learning achieved through on-the-job training and self-study and reading have been mentioned above. Formal in-house training courses provide a method for controlling content and the presentation of a course. These courses can easily be documented and the training materials for the courses can be reviewed to ensure input for individuals with the necessary qualifications and experience.

The methods of acquiring knowledge differed in the subgroups and were similar to those reported in the previous section. Respondents working for CROs mostly acquired their knowledge through on-the-job training and formal in-house training and to a lesser extent self-study and reading. University biostatisticians

learned through on-the-job training and those working for government research agencies primarily acquired knowledge through self-study and reading.

4.1.3.3 Clinical trial design

A clinical trial biostatistician provides input into the overall design of a clinical trial (Lewis et al, 1995; DeMets et al, 1994 and Pocock, 1995). This input includes providing recommendations regarding the type of clinical trial (superiority, equivalence), the most appropriate clinical trial design (parallel, cross-over), the type of outcome variables to be used (composite variables, global assessment variables) and calculation of the sample size (ICH, 1998b). The clinical trial biostatistician is also required to review the protocol and CRF, prepare the randomisation materials and provide input regarding interim analyses, DSMBs and avoiding bias (North, 1998).

Respondents had at least a theoretical knowledge in nearly all the topics included in this section. The topics in which respondents were the least familiar were statistical considerations for CRF design, interim analyses and DSMBs. CRF design is not a primary task of clinical trial biostatisticians although it is advisable that the clinical trial biostatistician learns to review this document for design features which may influence the final data analysis and the ability to combine data across trials. Few studies include an interim analysis or a DSMB hence the lack of familiarity of the clinical trial biostatisticians in these topics. However, these features are becoming more common-place in the industry. A clinical trial biostatistician should be included in planning for an interim analysis or the provision of data to DSMBs to ensure that the blinding and integrity of the final analysis results are maintained. Clinical trial biostatisticians lacking experience in the various aspects of clinical trial design should not be involved in design of a clinical trial prior to receiving the necessary training in these topics.

Nearly all clinical trial biostatisticians working in CROs showed at least a theoretical knowledge in various aspects of clinical trial design with the smallest proportion exhibiting knowledge in the statistical considerations for DSMBs.

Biostatisticians employed by government research agencies reported the next highest proportions of knowledge in these topics.

The topics with the lowest proportions in government research agencies were statistical considerations for protocol review, CRF design and DSMBs. University biostatisticians were generally less familiar with the topics than the other two subgroups. They reported the lowest proportion of biostatisticians being familiar with the statistical considerations for DSMBs, as observed in the other groups.

Knowledge and experience in the clinical trial design topics included in the questionnaire, except for sample size calculation, were mostly acquired through on-the-job training, self-study and reading, followed by formal in-house training. Concerns regarding these methods of acquiring knowledge were discussed previously. Respondents learned about sample size calculation through their university degree, on-the-job training and self-study and reading. It is notable that this topic is the only time that a university degree is one of the main methods of acquiring knowledge in one of the questionnaire topics. The acquisition of knowledge through a university degree ensures good control of the course content and recommended reading. Also university courses assess a student's level of learning. A disadvantage of a university course is that it can be too theoretical, not including a practical component in a course.

The methods of acquiring knowledge observed in the subgroups were similar to those reported in the previous section.

4.1.3.4 Data management

A clinical trial biostatistician is required to provide input into the data management processes in a clinical trial. This task includes providing input into the structure of the database, the data validation specifications and identifying critical data. The biostatistician is also expected to conduct a statistical review of a database prior to accepting it for analysis. In order to conduct these tasks the clinical trial biostatistician should have a thorough understanding of the data management process (Monti, 2001 and Grobler et al, 2001).

The reasonably high level of knowledge and experience in these topics is indicative of the fact that clinical trial biostatisticians are required to work with a database in order to generate and present the study results. Performing a statistical review of a database prior to accepting a database for analysis is a task that has only recently become more widely required and accepted in clinical trials, hence the lower level of knowledge and experience reported in this topic.

All the subgroups indicated a reasonably high proportion of clinical trial biostatisticians with at least a theoretical knowledge of data management for clinical trials and biostatistical input into data management processes. The proportion of biostatisticians with at least a theoretical knowledge of conducting the statistical review of a database was high in CROs and universities, and low in government research agencies.

As with previous groups of topics it appears that those respondents who indicated that they at least had a little knowledge/experience of a topic, acquired the knowledge through on-the-job training followed by self-study and reading and formal in-house training. The pitfalls of these methods of acquiring knowledge have been described previously. The benefits of self-study and reading are that they enable a person to acquire the required knowledge at the time at which it is required rather than waiting for formal training to be presented.

Clinical trial biostatisticians working in CROs generally acquired their knowledge in these data management topics through on-the-job training followed by formal in-house training. Those biostatisticians employed by universities and government research agencies learned through on-the-job training; with those in government research agencies acquiring knowledge through self-study and reading.

4.1.3.5 Statistical analysis considerations

Statistical analysis considerations that a clinical trial biostatisticians needs to take into account when analysing a clinical trial include: ensuring that different types of data are presented as required by international guidelines, deciding what data is valid for analysis, defining analyses before conducting them and considering missing data, outliers and covariates (Lewis et al, 1995; Senn, 1997 and Pong and Chow, 1997).

Respondents indicated that they have either a working knowledge or extensive experience in most of the considerations regarding the statistical analysis of clinical trials. The "statistical analysis of clinical trials" was the task in which the respondents reported they had the most experience.

The topics with which respondents reported being the least familiar were writing derived dataset specifications, conducting a data review meeting, international coding dictionaries and bioequivalence studies.

The writing of derived dataset specifications is a procedural task which helps to ensure sufficient planning goes into the derivation of data for using in tabulations and statistical tests. Such specifications also facilitate the validation of derived datasets (Monti, 2001).

The ICH E9 guideline (1998b) specifies that planned analyses and the determination of which data is valid for analysis should be finalised prior to unblinding the treatment assignments. The guideline suggests that this determination should be done after a blind review of this data. It is advisable to hold a data review meeting at which the data issues are discussed and the SAP and analysis populations are finalised.

International coding dictionaries are used to code adverse event, medical history, concomitant illness and medication data. In order to appropriately analyse, present and interpret the data a clinical trial biostatistician should have an understanding of the structure of such a dictionary and how terms are coded according to it.

Bioequivalence studies are a subset of phase I studies for which detailed analysis methods and requirements are laid down by regulatory authorities. In order to be responsible for the analysis of such studies a clinical trial biostatistician should have at least a theoretical knowledge in this topic (Senn, 1997).

Nearly all the CRO clinical trial biostatisticians have at least a theoretical knowledge in statistical analysis considerations as listed in the questionnaire. Fewer biostatisticians employed by government research agencies and university biostatisticians had experience in these topics than was reported for CRO biostatisticians. The topics with which government research agency biostatisticians are most familiar are the presentation and analysis of demographic and background data and other data analysis considerations such as covariates and interactions. University biostatisticians indicated that they were most knowledgeable with these topics.

Knowledge in statistical analysis considerations was mostly acquired through on-the-job training. Self-study and reading were the next most frequently used method of knowledge acquisition followed very closely by formal in-house training. Just over a third of the respondents indicated that they learned of data analysis considerations such as covariates and interactions through their university courses. Since the respondents have at least a three-year university qualification in statistics a higher proportion of learning through a university course would be expected for topics such as covariates and interactions. The benefits and disadvantages of using the different methods of learning have been discussed previously.

On-the-job training followed by formal in-house training were the most frequent methods of knowledge acquisition for CRO clinical trial biostatisticians. On-the-job training was mostly used to develop university biostatisticians in these topics and a mixture of on-the-job training, self-study and reading was used to train biostatisticians employed by government research agencies.

4.1.3.6 Statistical methods

Although clinical trial biostatisticians need to have a wide knowledge of the sphere in which they are applying statistical methodology, they also should be able to apply statistical principles and methods appropriately to clinical trials (DeMets et al, 1994 and Chuang-Stein, 1996).

Very few of the respondents indicated that they did not have at least a theoretical knowledge of statistical methods listed in the questionnaire, with the majority having either a working knowledge or extensive experience. The same results were observed in the subgroup analyses. As the respondents are university graduates with at least a bachelors degree majoring in statistics and working as biostatisticians this finding was as expected.

The statistical method with which respondents were the least familiar was survival analysis.

The respondents mostly acquired their knowledge through a university degree. Respondents have at least a bachelors degree majoring in statistics and almost all have a post-graduate degree in statistics. However, many of the respondents also learned about these statistical methods through on-the-job training and self-study and reading. Clinical trial biostatisticians, regardless of their employer, learned of these statistical methods primarily through their university education followed by on-the-job training. The on-the-job training offers the opportunity of introducing a practical component to the learning process.

4.1.3.7 Reporting

Once the analysis results have been presented in tables, listings and graphs, the clinical trial biostatistician is required to write or at least contribute to the clinical trial report. Ensuring the accurate interpretation of the statistical output and correct description of analytical issues and data handling requirements. The clinical trial biostatistician is one of the team finally responsible for the clinical trial report (ICH, 1998b and Cook, 1995).

Quite a number of the respondents were not familiar with the reporting topics. The ICH E9 guideline for Statistical Principles in Clinical Trials (1998b) includes details of what statistical information should be included in a clinical study report, and the ICH E3 guideline for the Structure and Content of Clinical Study Reports (1995) includes details on the layout and content of clinical trial reports. In all 10 (35%) of the respondents had little or no knowledge of writing/reviewing clinical study reports; acquisition of this knowledge starts with becoming familiar with the guidelines mentioned above. Once a clinical trial biostatistician is familiar with these documents learning basic scientific writing conventions is necessary. Writing and reviewing publications is not a task that is routinely conducted by all clinical trial biostatisticians but rather more senior and experienced clinical trial biostatisticians (Pocock, 1995).

Clinical trial biostatisticians employed by government research agencies are most familiar with medical writing conventions and the writing and reviewing of publications and CRO biostatisticians are most familiar with writing and reviewing clinical study reports.

Similarly to the results of the methods of acquiring knowledge in the previous sections the knowledge and experience in reporting topics were mostly acquired through on-the-job training, self-study and reading. Quite a number respondents also acquired knowledge through formal in-house training. On-the-job training featured as the leading method of acquiring knowledge in biostatisticians employed by CROs and universities and as a secondary method in biostatisticians employed by government research agencies. Formal in-house training was also used to train CRO biostatisticians in writing and reviewing clinical study reports. The primary method for becoming familiar with reporting topics for government research agency biostatisticians was self-study and reading.

4.1.3.8 Quality control and documentation

The internationally accepted GCP guideline (ICH, 1996b) requires that all study procedures should be sufficiently documented and checked for correctness. Quality control and review procedures need to be implemented by the clinical

trial biostatistician to ensure accurate representation of the data and results. A clinical trial biostatistician is required to know what study documentation should be retained by them and to ensure the paper and electronic archiving of these documents (North 1998).

Since GCP places such an emphasis on ensuring the correctness and appropriateness of statistical results, it is not ideal that 40% of respondents indicated that they had little or no knowledge of the quality control and documenting topics.

The majority of clinical trial biostatisticians employed by CROs are knowledgeable in all three quality control and documentation topics. Biostatisticians employed by universities and government research agencies were not as familiar with these topics.

The majority of the respondents acquired their knowledge and experience through on-the-job training, and this method of learning was primary in all three subgroups. It is unusual to learn of paper and electronic archiving through a university degree, although this fact was indicated by one of the respondents. In addition formal in-house training was also used to teach clinical trial biostatisticians employed by CROs.

Given the lack of knowledge and experience regarding these quality control and documentation topics in university departments and government research agencies it is advisable that on-the-job training would not be the most effective method of training to continue using in these institutions.

4.1.3.9 Computer skills/packages

All but one of the respondents are able to program in SAS® and all have at least a working knowledge of Microsoft Word. These programs are the pharmaceutical industry standard for analysis and reporting, respectively. Very few respondents have knowledge of or experience with nQuery, StatXact, WinNonLin and CIA. The lack of familiarity of respondents with StatXact and WinNonLin is associated with their lack of knowledge of exact tests and

bioequivalence, respectively. nQuery is a program used to calculate sample size and CIA is used to calculate confidence intervals. The knowledge and experience of clinical trial biostatisticians in the computer skills and packages listed in the questionnaire do not differ much between the subgroups.

Respondents mostly became familiar with SAS® through on-the-job training and self-study and reading. Quite a number of the respondents have attended formal in-house training in SAS® and a quarter of the respondents had learned of SAS® during their university courses. Microsoft Word and Excel were mostly learned through self-study and reading, followed closely by on-the-job training. About a third of respondents were taught about Microsoft Word and Excel during their university courses. Respondents became familiar with PowerPoint through self-study and reading followed by on-the-job training. As seen above, very few respondents acquired knowledge and experience in nQuery, StatXact, WinNonLin and CIA.

In the topics in which many of the respondents have either a working knowledge or extensive experience, on-the-job training coupled with self-study and reading provided an effective method of learning. The formal in-house training in SAS® may be a successful method of training if it incorporates a practical component.

4.1.3.10 Other appropriate topics

The majority of additional topics mentioned by the respondents relate to additional computer skills and packages. A few clinical trial design and statistical methods topics were also mentioned. Some of the topics such as the design and maintenance of a quality database and the International Standards Organisation are not necessarily directly related to clinical trial biostatisticians but can be aligned to delivery of a quality product.

4.1.3.11 Summary

The questionnaire sections in which respondents reported a good knowledge and experience were:

- The drug development process and clinical trials

- Clinical trial design
- Data management
- Statistical methods
- Computer skill and packages

The questionnaire sections in which respondents were less familiar were:

- Regulatory requirements and international guidelines
- Statistical analysis considerations
- Reporting
- Quality control and documentation

Overall knowledge and experience were mostly acquired through on-the-job training followed by self-study and reading. Thereafter the most frequent method of learning was formal in-house training with a few respondents indicating that they acquired their knowledge through a university degree. Very few respondents acquired their knowledge and experience through other training courses.

4.2 UNIVERSITY COURSE CONTENT SURVEY

4.2.1 Response rates

Twenty South African universities were approached to provide information regarding the statistics courses they presented. Information was obtained for fourteen (70.0%) of these universities. There was no response from six of the universities.

4.2.2 Number of undergraduate university statistics courses

A university was requested to provide details of all undergraduate statistics courses presented by their institution including part-time and full-time courses as well as any correspondence courses. South African Technikons and colleges were not approached since the EFSPI defined the basic requirement for an appropriately qualified clinical trial biostatistician as a three-year university course.

In South Africa an undergraduate degree, a bachelors degree, equates to three-years of full-time study. Thereafter a student may complete a fourth year known as an Honours degree. A university course is defined differently at the various South African universities. Courses range from three-month courses to full-year courses, but all courses are restricted to a specific year of study. Courses were counted as defined by each university and not normalised to be courses of equivalent length. Approximately half of the South African universities presented between four and seven first-, second- and third-year courses.

4.2.3 Content of undergraduate university statistics courses

Very few South African universities presented courses including topics outside of the Statistical Methods Section as identified on the clinical trial biostatistician questionnaire. The most frequently covered topics other than those under statistical methods were reported as:

- courses identified as having a computer usage component (in most cases the actual computer package used was not identified) – 10 of the 14 responding universities,
- courses covering quality control – 5 of the 14 responding universities, and
- projects which require students to collect, analyse and report data – 5 of the 14 responding universities.

Statistical methods that are included in first-year through to third-year courses by at least 12 universities are:

- Analysis of continuous data (which includes the comparison of continuous data, p-values, point estimates and confidence intervals),
- ANOVA/ANCOVA,
- Linear regression,
- Analysis of binary and categorical data (which includes the comparison of binary and categorical data, p-values, point estimates and confidence intervals),
- Non-parametric methods,
- Generalised linear models (only 10 universities all at a third-year course level)

Statistical methods that are included in courses from about half of the responding universities are:

- Repeated measures/multivariate analysis,
- Contingency tables,
- Logistic regression.

Analysis of survival data including Cox regression and Kaplan-Meier estimates was only included in a third of the third-year courses at the responding universities.

Statistical methods topics as identified on the clinical trial biostatistician questionnaire which are not well covered by courses presented by responding universities are:

- exact tests (not included in courses at any of the responding universities), and
- risk ratios/odds ratios/Mantel-Haenzel methods (mentioned by two of the 14 responding universities).

There is a possible overlap between the topics which were identified to be contained in the university courses. However, a course was only indicated as including a topic if the topic was expressly mentioned in the course description.

4.2.4 Discussion

The courses offered by responding universities include basic statistical methodology and computer skills. However, research methodology courses, courses covering clinical trial and experimental design and other statistical analysis considerations are not offered. There were also no courses specific to statistics for medical research. Epidemiology is primarily offered to health professionals in South Africa with such courses being taught in medical schools.

According to Zelen (2003) biostatisticians should be broadly trained in statistics, probability, computing and applied mathematics. They should be familiar with a

broad range of methodology, must have a sound knowledge of theory and must be capable data analysts.

Although it is not necessarily appropriate for statistics departments at South African universities to train students in all of the topics included in the questionnaire, given the small population of clinical trial biostatisticians in South Africa, they should at least provide students with the broad knowledge of the topics listed in the statistical methods section. Many of the topics appropriate for clinical trial biostatisticians are also of relevance to biostatisticians in general. Altman's book "Practical Statistics in Medical Research" (1991) covers most of the relevant methods and could thus be used as a general textbook in a biostatistics course.

Zelen (2003) also mentions that in training biostatisticians, students should be exposed to the application of biostatistics to real problems. Only five of the 14 universities particpating in the survey offer a "project" course which involves the collection, analysis, interpretation and reporting of data. The implementation of such a course at all universities offering a statistics programme would benefit the students in making the transition from the academic environment to the workplace. Such a course can also familiarise students with basic research methodology including how to write a protocol. It would also be preferable if these skills could be linked to a course in experimental design.

The proposal of such a "project" is supported by Greenhouse (2003) who when discussing biostatistics training says that a student should be faced with a variety of statistical problems and of statistical data, in order to lead him or her to appreciate that part of statistics which is more art than science, "to be able to get at the information in the data needed to answer a question, to summarise it, and to find optimal methods of analysis."

In order to develop the computing skills of students universities should promote the use of computers and preferably SAS® for assignments and the practical component of the courses. Tobi, Kuik, Bezemer and Ket (2001) propose computational science as one of the disciplines in which biostatisticians should

be trained. They define computational science as the critical use of standard statistical software, including the writing of custom macros and possibly developing computer software.

CHAPTER 5: CONCLUSIONS AND RECOMMENDATIONS

5.1 UNIVERSITY PROGRAMME

Ideally an undergraduate university programme might developed at a South African university specific to the training of clinical trial biostatisticians or medical statisticians on the whole. However, due to the small population of clinical trial biostatisticians and the relatively small job market for biostatisticians in South Africa, this proposal is not necessarily viable at this time.

Alternatively it may be more viable to develop an Honours or Masters Biostatistics programme to be taken by students completing a general statistics undergraduate programme. Some South African universities already offer such a course, for example, the University of Cape Town have a Biostatistics Honours course and the University of Fort Hare offers a Biostatistics Masters programme. The University of Stellenbosch is in the process of developing a post-graduate Biostatistics programme.

If a postgraduate programme is developed by a South African university it would be worthwhile to investigate the content of such programmes offered overseas. Tobi et al (2001) propose six disciplines for a curriculum for the consultation biostatistician: applied statistics, methodology, epidemiology, communication, computational science and personal effectiveness.

The following courses can be considered for inclusion in a post-graduate biostatistics programme:

- Biostatistics and epidemiology: Including statistical methods appropriate to biostatisticians. It is suggested that Altman's book, "Practical Statistics for Medical Research" (1991), may be used as a textbook for such a course.
- Techniques for (bio)statistical consulting: Including non-technical skills, for example, communication with clients, presentation skills and publication and report writing

- Clinical trials: Design of medical studies, with emphasis on randomized controlled clinical trials; analysis considerations for clinical trials including topics such as determining analysis populations
- Research methodology: Good clinical practice, ethics including consent and insurance, adverse drug reaction surveillance, randomization, data management, protocol preparation, case record forms and international guidelines for clinical research

In order to facilitate the development of such a university programme it is recommended that an industry representative (at least one specific to the clinical trial industry) be included on the Standards Generating Body for Statistics. SASA is in the process of working on the different aspects required for such a body (de Wet, 2003).

5.2 IMPROVEMENTS TO CURRENT UNIVERSITY COURSES

It is proposed that courses at South African universities should, at a minimum, include the statistical methods most applicable to clinical trial biostatisticians (see below for statistical methods not frequently included in courses). Furthermore, as many students as possible should be exposed to 'hands-on' data collection, analysis and reporting. Research methodology is a course usually presented only to students continuing with post-graduate studies; however, it is recommended that all statistics students, at least those intending to move into a research environment, should attend such a course. The universities should also include a computing component to their courses, and preferably should expose their students to SAS.

Important topics usually included in courses at South African universities are: ANOVA, linear regression, analysis of categorical and continuous data, non-parametric methods and generalised linear model. The statistical methods, which should be considered for inclusion in undergraduate courses are:

- Exact tests
- Risk ratios/odds ratios/Mantel-Haenszel methods
- Analysis of survival data

- Repeated measures/multivariate analysis
- Contingency tables
- Logistic regression

5.3 DEVELOPMENT OF A CLINICAL TRIAL BIOSTATISTICS MANUAL

Since clinical trial biostatisticians in South Africa are predominantly trained through on-the-job training, and self-study and reading, it is recommended that a comprehensive manual be developed to be used when conducting such training. On-the-job training and self-study both have limitations as a method of training because there is no control over the content and completeness of such training. A manual can be developed and reviewed by qualified and experienced clinical trial biostatisticians and thus overcome these limitations.

A proposed outline for such a manual could be as follows:

1. The Drug Development Process and Clinical Trials
    - 1.1 History and Rationale of Randomised Clinical Trials
    - 1.2 Drug Development Process
    - 1.3 Overview of Clinical Trials
    - 1.4 Clinical Trial Team
2. International Guidelines and Standard Operating Procedures
    - 2.1 ICH Guidelines
    - 2.2 Standard Operating Procedures
        - 2.2.1. CRO Standard Operating Procedures
        - 2.2.2. Sponsor Standard Operating Procedures
        - 2.2.3. PSI Standard Operating Procedures Guidance Documents
    - 2.3 Other Guidance Documents
3. Initiating a Project
    - 3.1 Organising Documentation
    - 3.2 The Project File
4. Clinical Trial Design
    - 4.1 Protocol Design
        - 4.1.1. Types of Clinical Trials
        - 4.1.2. Clinical Trial Designs

4.1.3. Outcome Variables
4.1.4. Sample Size Calculation
4.1.5. Blinding
4.1.6. Regulatory Requirements and Protocol Submission
4.2 CRF Design
4.2.1. Process of CRF Design
4.2.2. Design Considerations
4.3 Randomisation
4.3.1. Process of Randomisation
4.3.2. Randomisation Considerations
5. Role of a Biostatistician in the Clinical Conduct of a Trial
5.1 Data Safety Monitoring Boards
5.2 Interim Analyses
5.3 Protocol Amendments
6. Data Management Process
6.1 Role of a Biostatistician in Data Management
6.2 Data Management Plan
6.3 Statistical Review of a Database
7. Statistical Analysis [Cover at least all ICH topics]
7.1 Planning the Statistical Analysis
7.1.1. Statistical Analysis Plan
7.1.2. Table and Graph Templates
7.1.3. Statistical Output
7.2 Analysis Populations
7.3 Blind Review of Data
7.4 Analysing the Data
7.4.1. Types of Data
7.4.2. Presenting Data
7.4.3. Statistical Methods (include methods such as analysis of variance, Mantel-Haenszel method, Kruskal-Wallis, as appropriate)
7.4.4. Other Considerations (include considerations such as Covariates and missing data, as appropriate)
7.5 Programming Considerations and Documentation
8. Reporting

8.1 ICH Report Structure and Content
8.2 Annotated Report Outline
8.3 Appendices
8.4 Medical Writing Style/Conventions
8.5 Formatting
8.6 Review/Editing
8.7 Publications

9. Quality Control and Quality Assurance
   9.1 Quality Control and Senior Biostatistics Review
   9.2 Quality Assurance
   9.3 Signing-off Documents
10. Archiving
   10.1 Archiving Paper Documents
   10.2 Archiving Electronic Documents
11. References
12. Abbreviations
13. Terminology
14. Appendices
   14.1 Example of the Contents of a Project File
   14.2 Example of a Protocol
   14.3 Example of a CRF
   14.4 Example of a Randomisation Schedule and Related Documents
   14.5 Example of an Unblinding Plan
   14.6 Example of a Data Management Plan
   14.7 Example of a Statistical Analysis Plan and Templates
   14.8 Example of Blind Review Minutes
   14.9 Example of a Report (without Appendices)
   14.10 Example of a Quality Control plan
   14.11 Example of an Audit Checklist

Should such a manual be developed it is recommended that it be updated regularly, perhaps yearly, since many of the guidelines mentioned in the "International Guidelines and Standard Operating Procedures" section are being constantly updated and new guidelines are being written.

5.4 CERTIFICATION OF MEDICAL STATISTICIANS IN SOUTH AFRICA

The EFSPI Working Group (1999) discusses the development of a European certification scheme. However, due to various factors the implementation of such a scheme is not feasible for the short term. However, it is hoped that the European-wide definition of an appropriately qualified and experienced statistician being one with a three-year degree in statistics and at least three years of experience in medical statistics would make the implementation of such a scheme possible in the long-term (EFSPI, 1999).

Certification schemes are in place in the United Kingdom, Germany and Spain. The Netherlands is in the process of developing a certification scheme (EFSPI, 1999).

It is recommended that a certification scheme be developed and implemented in South Africa. Such a scheme should focus on the qualifications and experience of individuals. It should also specify the areas in which an applicant should be proficient. The implementation of such a scheme would promote confidence of employers and non-South Africans in the abilities of certified individuals. This certification should be an optional process by which individuals can achieve professional recognition for statistical knowledge and achievement. It should also be distinguished from the legal licensing of practitioners.

It should also be investigated if it would be possible to link up the certification of South African clinical trial biostatisticians with one of the certification programmes available in Germany, Spain and the United Kingdom.

5.5 CONCLUSION

The profile of clinical trial biostatisticians in South Africa, with respect to qualifications and experience, is comparable to clinical trial biostatisticians in Europe. However, the industries in which the biostatisticians are employed differ from those that employ clinical trial biostatisticians in Europe.

South African clinical trial biostatisticians are not necessarily familiar with all the topics applicable to their discipline. The areas in which they were the least familiar were: Regulatory requirements and international guidelines, statistical analysis considerations, reporting, and quality control and documentation. Aside from statistical methods which were mostly learned through a university degree, knowledge and experience were mostly acquired through on-the-job training followed by self-study and reading.

It is hoped that the implementation of a university programme specific to clinical trial biostatisticians, improvements in current statistical courses, the development of a clinical trial biostatistician manual and the introduction of a medical statistician certification scheme, would contribute to developing what Iman (1995) is referring to when he quotes Kettenring in saying, "Industry needs holistic statisticians who are nimble problem solvers".

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APPENDICES

APPENDIX A: INSTITUTIONS CONTACTED TO IDENTIFY CLINICAL TRIAL BIOSTATISTICIANS

Department	University/Company
Department of Mathematics and Statistics	MEDUNSA
School of Computer, Statistical & Mathematical Sciences	PU of CHE
Department of Mathematics and Statistics	Rand Afrikaans University
Department of Statistics	Rhodes University
Department of mathematical Statistics and Statistics	University of the Free State
Department of Statistical Sciences	University of Cape Town
Department of Statistics	University of Durban-Westville
Department of Statistics	University of Fort hare
School of Mathematical and Statistical Sciences	University of Natal (Durban)
School of Mathematics, Statistics and Information Technology	University of Natal (Pietermaritzburg)
Department of Mathematical Statistics	University of Port Elizabeth
Department of Statistics	University of Pretoria
Department Statistics and Actuarial Science	University of Stellenbosch
Department of Statistics	UNISA
Department of Statistics and Operations Research	University of the North
Department of Statistics	University of the North West
Department of Statistics	University of the Western Cape
School of Statistics and Actuarial Science	University of the Witwatersrand
Department of Statistics, Faculty of Science	University of Transkei
Department of Mathematical Statistics	University of Zululand
Department of Mathematical Statistics	Vista University
Biopharmaceutics Research Institute	Rhodes University
Biostatistics Unit	Medical Research Council
Department of Biostatistics	University of the Free State
Department of Biostatistics	Qdot-pharma
Department of Biometry	Farmovs-parexel
Head Office	Stats SA
Biostatistics Department	Perinatal HIV Research Unit
Contract Research Unit	Wits Health Consortium
-	Medicines Control Council
Human Resources	Department of Health
Faculty of Health Sciences	University of Transkei
Faculty of Medicine	MEDUNSA
Faculty of Health Sciences	University of Cape Town
Faculty of Health Sciences	University of Stellenbosch
Faculty of Health Sciences	University of the Free State
Faculty of Health Sciences	University of Pretoria
Wits Medical School	University of the Witwatersrand
Faculty of Health Sciences	University of Natal (Durban)
Director Research Focus Area	Drug Research and Development
Faculty of Health Sciences	Rhodes University
Faculty of Health Sciences	University of Port Elizabeth
Biostatistics department	Quintiles ClinData

Note: This list does not include pharmaceutical companies that were contacted nor the affiliations of persons on the SASA Consultants list.

APPENDIX B: LETTER TO IDENTIFY CLINICAL TRIAL BIOSTATISTICIANS

Note: The pages in this appendix have been reduced in size for technical reasons

LETTER TO IDENTIFY CLINICAL TRIAL BIOSTATISTICIANS

Dear Sir or Madam:

A survey is being performed to profile clinical trial biostatisticians in South Africa. This survey is being conducted as part of an M.Med.Sc degree through the Biostatistics Department of the University of the Free State. It intends to assess the education/training profile of clinical trial biostatisticians in South Africa and to assess the knowledge of biostatisticians in areas considered necessary to be an appropriately qualified and experienced clinical trial biostatistician as accepted internationally. An abstract of the research proposal and the rationale behind the research are included as an attachment to this letter. Please take time to read the included information carefully and feel free to ask for more information if required.

Your assistance is needed to identify **clinical trial biostatisticians**, *i.e. statisticians responsible for providing statistical input at any stage of a clinical trial (studies that evaluate investigational medicines, medical disease prevention, diagnostic techniques and treatments), from the design through to the final study report.* These clinical trial biostatisticians will be contacted and asked to complete a questionnaire re their qualifications, experience and training. If you are aware of people who fulfil the role of a clinical trial biostatistician (either on a part-time or full-time basis) please could you provide me with their contact details. A table has been included below in which to complete the details required; please provide as complete details as is possible to ensure that we are able to include as many people in the survey as possible. Please either return the table by email or by fax to the candidate (contact details are provided below). If you are not aware of any clinical trial biostatisticians please inform the candidate of this by email, fax or telephone.

Please note that participation in the survey is voluntary. Respondents will not have to participate in the survey if they do not wish to and if they decide not to participate, they do not have to give a reason for their decision. Any records identifying a respondent will be kept confidential and will not be made publicly available. The information collected during the survey will be stored in paper files and on computer databases, but names will not. Only the candidate and his/her supervisor will know that the information is related to a respondent. The results of the survey may be published in literature, but identities will not be revealed.

Kind regards,
Sharon Rossouw

Contact details should you require further information

Supervisor:
Prof. Gina Joubert,
Dept of Biostatistics, University of the Free State,
Tel: 051 – 401 3117,
Email: gnbsgj@med.uovs.ac.za

Candidate:
Ms. Sharon Rossouw,
PO Box 13942, Noordstad, 9301
Tel: 051 – 401 4929,
Email: Sharon.Rossouw@Quintiles.com

LETTER TO IDENTIFY CLINICAL TRIAL BIOSTATISTICIANS

Contact details required for clinical trial biostatisticians

Name (incl. title)		Name (incl. title)	
Institution		Institution	
Address		Address	
Telephone number		Telephone number	
Email address		Email address	

Name (incl. title)		Name (incl. title)	
Institution		Institution	
Address		Address	
Telephone number		Telephone number	
Email address		Email address	

Name (incl. title)		Name (incl. title)	
Institution		Institution	
Address		Address	
Telephone number		Telephone number	
Email address		Email address	

Name (incl. title)		Name (incl. title)	
Institution		Institution	
Address		Address	
Telephone number		Telephone number	
Email address		Email address	

Name (incl. title)		Name (incl. title)	
Institution		Institution	
Address		Address	
Telephone number		Telephone number	
Email address		Email address	

Name (incl. title)		Name (incl. title)	
Institution		Institution	
Address		Address	
Telephone number		Telephone number	
Email address		Email address	

Name (incl. title)		Name (incl. title)	
Institution		Institution	
Address		Address	
Telephone number		Telephone number	
Email address		Email address	

APPENDIX: ABSTRACT OF THE RESEARCH PROPOSAL AND RATIONALE BEHIND THE RESEARCH

Abstract

Many statistical issues in the area of Phase II to Phase IV clinical trials are specific to this particular field. A clinical trial biostatistician should not only be appropriately qualified in general statistical theory, but also be appropriately trained and experienced in the application of statistics in clinical trials. This thesis will profile the background and training of statisticians practicing in this field in South Africa. It also aims to provide an overview of the training that is available for clinical trial biostatisticians at universities in South Africa. Lastly, the thesis will provide an outline for a comprehensive manual and training programme to be developed for clinical trial biostatisticians.

The methodology used for this research will include a literature study regarding the required profile (education/training, years of experience and part of the industry in which they are employed) of a clinical trial biostatistician, and topics of interest to such a biostatistician. A review of the content of courses offered at South African Universities will be performed including a comparison between mathematical statistics courses and biostatistical courses, where appropriate. A questionnaire survey will be carried out to assess the education/training profile of clinical trial biostatisticians in South Africa and to assess the knowledge of biostatisticians in areas considered necessary to be an appropriately qualified and experienced clinical trial biostatistician as defined in the literature.

Rationale

An understanding of the profile (education/training, knowledge, years of experience, part of the industry in which they are employed) of clinical trial biostatisticians internationally and how biostatisticians in South Africa compare with this profile will yield many benefits. It will enable employers to recruit and train new biostatisticians effectively and to develop their existing biostatisticians in any areas that training needs may be identified. Individual biostatisticians will be able to identify topics in which to undergo further training, if necessary.

An assessment of the training needs of clinical trial biostatisticians in South Africa and how these needs compare to what is offered at South African universities will enable the universities to identify how they can better serve the pharmaceutical industry. This can also contribute to the development of an outline to a comprehensive manual or training programme to accommodate the learning needs of a clinical trial biostatistician and may subsequently be used in either a university or business context.

APPENDIX C: CLINICAL TRIAL BIOSTATISTICIAN QUESTIONNAIRE

Note: The pages in this appendix have been reduced in size for technical reasons.

PROFILE OF CLINICAL TRIAL BIOSTATISTICIANS IN SOUTH AFRICA Respondent No: XXX

General information

You are invited to participate in a survey of the profile of clinical trial biostatisticians in South Africa. This survey is being conducted as part of an M.Med.Sc degree through the Biostatistics Department of the University of the Free State. Please take time to read the following information carefully and feel free to ask for more information if required. An abstract of the research proposal and the rationale behind the research are included as an appendix to this questionnaire.

You have been identified as a **clinical trial biostatistician**, *i.e. a statistician (full-time, part-time or occasional) responsible for providing statistical input at any stage of a clinical trial (studies that evaluate medicines, medical disease prevention, diagnostic techniques and medical treatments), from the design through to the final study report.* This survey intends to assess the education/training profile of clinical trial biostatisticians in South Africa and to assess the knowledge of biostatisticians in areas considered necessary to be an appropriately qualified and experienced clinical trial biostatistician as accepted internationally.

What will happen if you take part?

If you agree to participate in this survey you will be required to complete this questionnaire (either electronically or on hard-copy after printing it out) and return it before *12 July, 2003*. The questionnaire may be returned by faxing it to (051) 401-4999 or emailing it to Sharon.Rossouw@Quintiles.com. Please note that should you prefer to complete the questionnaire on hard-copy and return it by post, please contact me (contact details are provided below) and I will provide you with a stamped addressed envelope.

What if you do not wish to take part or if you have been wrongly identified as a clinical trial biostatistician?

Your participation in the survey is voluntary. You do not have to participate in the survey if you do not wish to and if you decide not to participate, you do not have to give a reason for your decision. Should you not wish to take part or if you have been wrongly identified as a clinical trial biostatistician please contact Prof. Gina Joubert, providing your respondent number as detailed on this questionnaire (top right corner) and informing her of your wish not to participate/incorrect identification. This will ensure that you will not be included in any follow-up contacts. Contact details are provided below.

Will the information given be confidential?

Any records identifying you will be kept confidential and will not be made publicly available. The information collected during the survey will be stored in paper files and on computer databases, but your name will not. Only the the supervisor and I will know that the information is related to you. Summary results of the survey may be published in literature, but individual data or your identity will not be revealed.

Who to contact should you require further information

Supervisor:
Prof. Gina Joubert,
Dept of Biostatistics, University of the Free State,
Tel: 051 – 401 3117,
Email: gnbsgj@med.uovs.ac.za

Candidate:
Ms. Sharon Rossouw,
PO Box 13942, Noordstad, 9301
Tel: 051 – 401 4929,
Email: Sharon.Rossouw@Quintiles.com

Please note the following when completing the questionnaire

- Some questions will require you to cross only one option, while others require you to cross all options that apply
- If you are completing the questionnaire electronically please note the following:
  - Please adjust your view layout in MS Word and the percentage viewing size to ensure that you can easily view the questions and answer options while completing the questionnaire (if you have a small screen/setting use 75 to 80%)
  - Please note that 'Page up' and 'Page down' are used to move between response fields, and cannot be used to move up and down in this document – to move up and down please use the scroll-bar on the right of your screen
  - You may cross a box (eg, ☐) by clicking on the box once
  - To un-cross a box click on the crossed box (eg, ☒) once
  - Comments can be typed into fields such as this one _____ by clicking on the field and typing the relevant information
  - Please save the questionnaire incorporating your responses and return the updated questionnaire as an email attachment or print it out and fax it to the number provided above.

PROFILE OF CLINICAL TRIAL BIOSTATISTICIANS IN SOUTH AFRICA Respondent No: XXX

1 QUALIFICATIONS AND EXPERIENCE

What is your highest qualification? *(Cross only one box)*

- ☐ First-year university course
- ☐ Second-year university course
- ☐ Bachelors degree
- ☐ Honours degree
- ☐ Masters degree
- ☐ PhD
- ☐ Other, specify:

What was your field of study?:

What is your highest statistics[1] qualification? *(Cross only one box)*

- ☐ First-year university course
- ☐ Second-year university course
- ☐ Bachelors degree
- ☐ Honours degree
- ☐ Masters degree
- ☐ PhD
- ☐ Other, specify:

[1] – Statistics, mathematical statistics, biostatistics or equivalent

Which part of industry do you *currently* work in as a clinical trial biostatistician? *(Cross only one box)*

- ☐ Pharmaceutical company
- ☐ Contract research organisation
- ☐ Government regulatory authority (MCC)
- ☐ University research/statistics department
- ☐ Government research agency (MRC, Statistics SA)
- ☐ Private
- ☐ Other, specify:

In which of the following industries have you worked before as a clinical trial biostatistician? *(Cross all that apply)*

- ☐ Pharmaceutical company
- ☐ Contract research organisation
- ☐ Government regulatory authority (MCC)
- ☐ University research/statistics department
- ☐ Government research agency (MRC, Statistics SA)
- ☐ Private
- ☐ Other, specify:

PROFILE OF CLINICAL TRIAL BIOSTATISTICIANS IN SOUTH AFRICA Respondent No: XXX

In which of the following do you have experience? ***(Cross all that apply)***

☐	Writing clinical development plans[1]	☐	Writing clinical trial protocols[2]
☐	Designing case report forms[3]	☐	Statistical analysis[4] of a clinical trial
☐	Writing clinical trial reports[5]	☐	Sample size calculation
☐	Preparation of randomisation materials[6]	☐	Preparation/review of data management plans[7]
☐	Other, specify:		

[1] – Clinical development plan = An ordered programme of clinical trials each with its own specific objectives
[2] – Clinical trial protocol = A document used to describe the objectives, design, methodology, statistical considerations and organisation of a clinical trial
[3] – Case report form = An instrument for collecting data in clinical trials
[4] – Statistical analysis = Conducting the analysis and presentation of data collected during a clinical trial
[5] – Clinical trial report = A compendium of a discussion regarding the objectives, design, methodology, statistical considerations and organisation of a trial, the presentation of the results of the clinical trial, a statistical discussion of the trial product's overall efficacy and safety and the clinical interpretation of these results
[6] – Randomisation materials = A sequential list of treatments (or treatment sequences) or corresponding codes by subject number, this may also include code-break envelopes
[7] – Data management plans = a set of data management documents developed prior to the initiating of data processing activities to detail the procedures that will be followed for each of the data management tasks

How many years of experience do you have as a biostatistician (not necessarily analysing clinical trials)?		years
What percentage of your working time do you spend working as a clinical trial biostatistician?		%
On average, how many clinical trials do you analyse in a year?		clinical trials
When did you last contribute to a clinical trial?	Month	Year

Which of the following phases of clinical trials have you analysed? ***(Cross all that apply)***

☐	Phase I[1]	☐	Phase II[2]
☐	Phase III[3]	☐	Phase IV[4]

[1] – Phase I clinical trials are the first trials performed in humans and often these trials are conducted without any therapeutic benefit to the subject
[2] – Phase II clinical trials are generally conducted in patients with the disease or condition of interest and look for indications of efficacy and continued safety of the treatment
[3] – Phase III clinical trials are conducted to prove efficacy to a regulator and provide further information regarding the safety and tolerability of the treatment. This is usually done by conducting large trials with more than one treatment arm in the patient population for which the treatment is eventually intended.
[4] – These Phase IV trials are performed in real-world conditions once a drug has been approved and can be used to detect rare and long-term side-effects or interactions, and to assess effects in different patient populations

2 KNOWLEDGE/EXPERIENCE

In each section, please indicate the topics in which you have knowledge/experience *(also complete the section detailing how you attained this knowledge/experience).*

The drug development process and clinical trials	**What knowledge/ experience do you have in this topic?** *(cross one)*					**How did you attain this knowledge/experience?** *(cross all that apply)*				
	No knowledge/ experience	Little knowledge/ experience	Theoretical knowledge only	Working knowledge	Extensive experience	University degree	On-the-job training	Formal in-house training	Self-study/reading	Other training course
History and rationale of randomised clinical trial	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Drug development process	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Conduct of a clinical trial	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Clinical trial team (the personnel involved in conducting a clinical trial)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Regulatory requirements and international guidelines	**What knowledge/ experience do you have in this topic?** *(cross one)*					**How did you attain this knowledge/experience?** *(cross all that apply)*				
	No knowledge/ experience	Little knowledge/ experience	Theoretical knowledge only	Working knowledge	Extensive experience	University degree	On-the-job training	Formal in-house training	Self-study/reading	Other training course
ICH[1] E3 – Structure and content of clinical study reports	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
ICH E6 – Good clinical practice	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
ICH E9 – Statistical principles for clinical trials	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
ICH E10 –Choice of control group in clinical trials	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
PSI[2] SOP[3] guidance documents	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
21 CFR Part 11 – Electronic records and electronic signatures	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Regulatory submission process	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

[1] ICH = International Committee on Harmonisation
[2] PSI = Statisticians in the Pharmaceutical Industry Limited
[3] SOP = Standard Operating Procedure

PROFILE OF CLINICAL TRIAL BIOSTATISTICIANS IN SOUTH AFRICA Respondent No: XXX

Clinical trial design	**What knowledge/ experience do you have in this topic?** *(cross one)*					**How did you attain this knowledge/experience?** *(cross all that apply)*				
	No knowledge/ experience	Little knowledge/ experience	Theoretical knowledge only	Working knowledge	Extensive experience	University degree	On-the-job training	Formal in-house training	Self-study/reading	Other training course
Types of clinical trials (superiority, equivalence, non-inferiority, etc.)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Clinical trial designs (parallel, cross-over, dose-response studies, etc)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Types of outcome variables (composite variables, etc)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sample size calculation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Statistical considerations for protocol review (including protocol amendments)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Randomisation and blinding (generating randomisation plans and preparing related documents)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Statistical considerations for CRF design	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Statistical considerations for interim analyses	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Statistical considerations for Data Safety Monitoring Boards[1]	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Avoiding bias in clinical trials	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

[1] A committee established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify or stop a trial

Data management	**What knowledge/ experience do you have in this topic?** *(cross one)*					**How did you attain this knowledge/experience?** *(cross all that apply)*				
	No knowledge/ experience	Little knowledge/ experience	Theoretical knowledge only	Working knowledge	Extensive experience	University degree	On-the-job training	Formal in-house training	Self-study/reading	Other training course
Data management for clinical trials	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Biostatistical input into data management processes	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Conducting the statistical review of a database	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

PROFILE OF CLINICAL TRIAL BIOSTATISTICIANS IN SOUTH AFRICA Respondent No: XXX

Statistical analysis considerations	**What knowledge/ experience do you have in this topic?** *(cross one)*					**How did you attain this knowledge/experience?** *(cross all that apply)*				
	No knowledge/ experience	Little knowledge/ experience	Theoretical knowledge only	Working knowledge	Extensive experience	University degree	On-the-job training	Formal in-house training	Self-study/reading	Other training course
Writing statistical analysis plans	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Writing derived dataset specifications	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Identifying analysis populations	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Conducting a blind review of data	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Presentation/analysis of demographic and background data	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Presentation/analysis of laboratory data	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Presentation/analysis of adverse events	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Presentation/analysis of concomitant illnesses and medication, medical history and previous medications	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Data analysis considerations (covariates, interactions, etc)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
International medical coding dictionaries	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Programming considerations and documentation (Good programming practices)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Pharmacokinetics and Pharmacodynamics	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Bioequivalence studies	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

PROFILE OF CLINICAL TRIAL BIOSTATISTICIANS IN SOUTH AFRICA Respondent No: XXX

Statistical methods	**What knowledge/ experience do you have in this topic?** *(cross one)*					**How did you attain this knowledge/experience?** *(cross all that apply)*				
	No knowledge/ experience	Little knowledge/ experience	Theoretical knowledge only	Working knowledge	Extensive experience	University degree	On-the-job training	Formal in-house training	Self-study/reading	Other training course
Analysis of continuous data	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
ANOVA/ANCOVA	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Linear regression	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Repeated measures/Multivariate analysis	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Non-parametric methods	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Analysis of binary and categorical data	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Contingency tables	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Risk ratios / odds ratios / Mantel-Haenzel method	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Logistic regression	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Generalised linear models	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Exact tests	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Analysis of survival data (incl. Cox regression, Kaplan-Meier estimates)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Reporting	**What knowledge/ experience do you have in this topic?** *(cross one)*					**How did you attain this knowledge/experience?** *(cross all that apply)*				
	No knowledge/ experience	Little knowledge/ experience	Theoretical knowledge only	Working knowledge	Extensive experience	University degree	On-the-job training	Formal in-house training	Self-study/reading	Other training course
Medical writing (scientific writing) style and conventions	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Writing/reviewing publications	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Writing/reviewing clinical study report	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

PROFILE OF CLINICAL TRIAL BIOSTATISTICIANS IN SOUTH AFRICA Respondent No: XXX

Quality control and documentation	**What knowledge/ experience do you have in this topic?** *(cross one)*					**How did you attain this knowledge/experience?** *(cross all that apply)*				
	No knowledge/ experience	Little knowledge/ experience	Theoretical knowledge only	Working knowledge	Extensive experience	University degree	On-the-job training	Formal in-house training	Self-study/reading	Other training course
Quality control and review processes	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Maintaining project documentation (including version control etc)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Paper and electronic archiving	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Computer skills/packages	**What knowledge/ experience do you have in this topic?** *(cross one)*					**How did you attain this knowledge/experience?** *(cross all that apply)*				
	No knowledge/ experience	Little knowledge/ experience	Theoretical knowledge only	Working knowledge	Extensive experience	University degree	On-the-job training	Formal in-house training	Self-study/reading	Other training course
MS Word	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
MS Excel	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
MS PowerPoint	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
NQuery	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
StatXact	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
WinNonLin	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
SAS	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
CIA	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Other appropriate topics	**What knowledge/ experience do you have in this topic?** *(cross one)*					**How did you attain this knowledge/experience?** *(cross all that apply)*				
	No knowledge/ experience	Little knowledge/ experience	Theoretical knowledge only	Working knowledge	Extensive experience	University degree	On-the-job training	Formal in-house training	Self-study/reading	Other training course
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
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	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

APPENDIX: ABSTRACT OF THE RESEARCH PROPOSAL AND RATIONALE BEHIND THE RESEARCH

Abstract

Many statistical issues in the area of Phase II to Phase IV clinical trials are specific to this particular field. A clinical trial biostatistician should not only be appropriately qualified in general statistical theory, but also be appropriately trained and experienced in the application of statistics in clinical trials. This thesis will profile the background and training of statisticians practicing in this field in South Africa. It also aims to provide an overview of the training that is available for clinical trial biostatisticians at universities in South Africa. Lastly, the thesis will provide an outline for a comprehensive manual and training programme to be developed for clinical trial biostatisticians.

The methodology used for this research will include a literature study regarding the required profile (education/training, years of experience and part of the industry in which they are employed) of a clinical trial biostatistician, and topics of interest to such a biostatistician. A review of the content of courses offered at South African Universities will be performed including a comparison between mathematical statistics courses and biostatistical courses, where appropriate. A questionnaire survey will be carried out to assess the education/training profile of clinical trial biostatisticians in South Africa and to assess the knowledge of biostatisticians in areas considered necessary to be an appropriately qualified and experienced clinical trial biostatistician as defined in the literature.

Rationale

An understanding of the profile (education/training, knowledge, years of experience, part of the industry in which they are employed) of clinical trial biostatisticians internationally and how biostatisticians in South Africa compare with this profile will yield many benefits. It will enable employers to recruit and train new biostatisticians effectively and to develop their existing biostatisticians in any areas that training needs may be identified. Individual biostatisticians will be able to identify topics in which to undergo further training, if necessary.

An assessment of the training needs of clinical trial biostatisticians in South Africa and how these needs compare to what is offered at South African universities will enable the universities to identify how they can better serve the pharmaceutical industry. This can also contribute to the development of an outline to a comprehensive manual or training programme to accommodate the learning needs of a clinical trial biostatistician and may subsequently be used in either a university or business context.

APPENDIX D: TESTER'S QUESTIONNAIRE

Note: The pages in this appendix have been reduced in size for technical reasons.

QUESTIONNAIRE TESTING Tester No: 05

General information

You are invited to participate in the testing of a questionnaire being used in a survey of the profile of clinical trial biostatisticians in South Africa. The survey is being conducted as part of an M.Med.Sc degree through the Biostatistics Department of the University of the Free State. Please take time to read the following information carefully and feel free to ask for more information if required. An abstract of the research proposal and the rationale behind the research are included as an appendix to this questionnaire. This survey intends to assess the education/training profile of clinical trial biostatisticians in South Africa and to assess the knowledge of biostatisticians in areas considered necessary to be an appropriately qualified and experienced clinical trial biostatistician as accepted internationally.

What will happen if you take part?

If you agree to participate in testing the questionnaire for this survey you will be provided with a copy of the questionnaire to be tested. You will be required to complete the survey questionnaire and indicate you interpretation of questions and your overall comments as prompted by the questions on the next few pages and return this testing response document before ***6 June, 2003***. The testing responses may be returned to Sharon Rossouw.

What if you do not wish to take part?

Your participation in this testing process is voluntary. Should you not wish to take part please contact Sharon Rossouw, and inform her of your wish not to participate. Contact details are provided below.

Will the information given be confidential?

Any records identifying you will be kept confidential and will not be made publicly available. The information collected during the testing process will be stored in paper files, but your name will not. Your responses only will be used to elicit possible changes to the final survey questionnaire and will not be included in the final survey results.

Who to contact should you require further information

Supervisor:
Prof. Gina Joubert,
Dept of Biostatistics, University of the Free State,
Tel: 051 – 401 3117,
Email: gnbsgj@med.uovs.ac.za

Candidate:
Ms. Sharon Rossouw,
PO Box 13942, Noordstad, 9301
Tel: 051 – 401 4929,
Email: Sharon.Rossouw@Quintiles.com

QUESTIONNAIRE TESTING Tester No: 05

1 OVERALL RESPONDENT REACTION

(Please cross the relevant response)

1.1	I found the questionnaire simple to use	Disagree	①	②	③	④	⑤ Agree
1.2	I could complete the questionnaire without paging back to the instructions	Disagree	①	②	③	④	⑤ Agree
1.3	The tone of the questionnaire was	Hostile	①	②	③	④	⑤ Friendly
1.5	Completing the questionnaire was	Difficult	①	②	③	④	⑤ Easy
1.6	The general information page explained the purpose of the research sufficiently	Disagree	①	②	③	④	⑤ Agree

2 QUESTIONNAIRE LAYOUT

(Please cross the relevant response)

2.1	The font used was	Hard to read	①	②	③	④	⑤ Easy to read
2.2	The font size was	Too small	①	②	③	④	⑤ Too large
2.3	Were the section divisions helpful?	Not at all	①	②	③	④	⑤ Very much
2.4	Were the footnotes helpful?	Not at all	①	②	③	④	⑤ Very much
2.5	Instructions on completing the questionnaire were	Confusing	①	②	③	④	⑤ Clear

3 TERMINOLOGY AND CONTENT

(Please cross the relevant response)

3.1	Terms I did not understand were explained in footnotes	Disagree	①	②	③	④	⑤ Agree
3.2	The response options were sufficient	Disagree	①	②	③	④	⑤ Agree
3.3	The questions asked were appropriate to the topic under investigation	Not at all	①	②	③	④	⑤ Very much
3.4	The questions were	Vague	①	②	③	④	⑤ Specific

QUESTIONNAIRE TESTING Tester No: 05

4 GENERAL COMMENTS

In this section, please comment freely on difficulties that you experienced when completing the questionnaire *(please reference the relevant section of the questionnaire if possible).* Please list any terms that you did not understand and mention anything that you felt was unclear – In the instructions, questions or response categories.

APPENDIX: ABSTRACT OF THE RESEARCH PROPOSAL AND RATIONALE BEHIND THE RESEARCH

Abstract

Many statistical issues in the area of Phase II to Phase IV clinical trials are specific to this particular field. A clinical trial biostatistician should not only be appropriately qualified in general statistical theory, but also be appropriately trained and experienced in the application of statistics in clinical trials. This thesis will profile the background and training of statisticians practicing in this field in South Africa. It also aims to provide an overview of the training that is available for clinical trial biostatisticians at universities in South Africa. Lastly, the thesis will provide an outline for a comprehensive manual and training programme to be developed for clinical trial biostatisticians.

The methodology used for this research will include a literature study regarding the required profile (education/training, years of experience and part of the industry in which they are employed) of a clinical trial biostatistician, and topics of interest to such a biostatistician. A review of the content of courses offered at South African Universities will be performed including a comparison between mathematical statistics courses and biostatistical courses, where appropriate. A questionnaire survey will be carried out to assess the education/training profile of clinical trial biostatisticians in South Africa and to assess the knowledge of biostatisticians in areas considered necessary to be an appropriately qualified and experienced clinical trial biostatistician as defined in the literature.

Rationale

An understanding of the profile (education/training, knowledge, years of experience, part of the industry in which they are employed) of clinical trial biostatisticians internationally and how biostatisticians in South Africa compare with this profile will yield many benefits. It will enable employers to recruit and train new biostatisticians effectively and to develop their existing biostatisticians in any areas that training needs may be identified. Individual biostatisticians will be able to identify topics in which to undergo further training, if necessary.

An assessment of the training needs of clinical trial biostatisticians in South Africa and how these needs compare to what is offered at South African universities will enable the universities to identify how they can better serve the pharmaceutical industry. This can also contribute to the development of an outline to a comprehensive manual or training programme to accommodate the learning needs of a clinical trial biostatistician and may subsequently be used in either a university or business context.

APPENDIX E: LETTER TO UNIVERSITIES TO OBTAIN COURSE CURRICULA

Note: The pages in this appendix have been reduced in size for technical reasons.

REQUEST FOR COURSE CURRICULA 19 May 2003

Dear Professor:

Research is being conducted to assess the education/training profile of clinical trial biostatisticians in South Africa and to assess the knowledge of biostatisticians in areas considered necessary to be an appropriately qualified and experienced clinical trial biostatistician as accepted internationally. This research is being conducted as part of an M.Med.Sc degree through the Biostatistics Department of the University of the Free State. Please take time to read the following information carefully and feel free to ask for more information if required. An abstract of the research proposal and the rationale behind the research are included as an attachment to this letter.

Part of the research being conducted is a review of the content of statistics, mathematical statistics and biostatistics courses offered at South African Universities. In order to perform this review, courses from various universities will be broken down into components identified in the curricula and summarized according to similar terms. Please could you provide curricula of the courses offered by your department, either electronically by emailing the information to Sharon.Rossouw@Quintiles.com, or by placing a hard-copy of the information in the stamped pre-addressed envelope and posting the envelope.

Any records identifying a university will be kept confidential and will not be made publicly available. The information collected during the survey will be stored in paper files and on computer databases, but the university's name will not. Only the candidate and his/her supervisor will know that the information is related to a specific university. The results of the survey may be published in literature, but a university's identity will not be revealed.

Kind regards,

Sharon Rossouw

Contact details should you require further information

Supervisor:
Prof. Gina Joubert,
Dept of Biostatistics, University of the Free State,
Tel: 051 – 401 3117,
Email: gnbsgj@med.uovs.ac.za

Candidate:
Ms. Sharon Rossouw,
PO Box 13942, Noordstad, 9301
Tel: 051 – 401 4929,
Email: Sharon.Rossouw@Quintiles.com

APPENDIX: ABSTRACT OF THE RESEARCH PROPOSAL AND RATIONALE BEHIND THE RESEARCH

Abstract

Many statistical issues in the area of Phase II to Phase IV clinical trials are specific to this particular field. A clinical trial biostatistician should not only be appropriately qualified in general statistical theory, but also be appropriately trained and experienced in the application of statistics in clinical trials. This thesis will profile the background and training of statisticians practicing in this field in South Africa. It also aims to provide an overview of the training that is available for clinical trial biostatisticians at universities in South Africa. Lastly, the thesis will provide an outline for a comprehensive manual and training programme to be developed for clinical trial biostatisticians.

The methodology used for this research will include a literature study regarding the required profile (education/training, years of experience and part of the industry in which they are employed) of a clinical trial biostatistician, and topics of interest to such a biostatistician. A review of the content of courses offered at South African Universities will be performed including a comparison between mathematical statistics courses and biostatistical courses, where appropriate. A questionnaire survey will be carried out to assess the education/training profile of clinical trial biostatisticians in South Africa and to assess the knowledge of biostatisticians in areas considered necessary to be an appropriately qualified and experienced clinical trial biostatistician as defined in the literature.

Rationale

An understanding of the profile (education/training, knowledge, years of experience, part of the industry in which they are employed) of clinical trial biostatisticians internationally and how biostatisticians in South Africa compare with this profile will yield many benefits. It will enable employers to recruit and train new biostatisticians effectively and to develop their existing biostatisticians in any areas that training needs may be identified. Individual biostatisticians will be able to identify topics in which to undergo further training, if necessary.

An assessment of the training needs of clinical trial biostatisticians in South Africa and how these needs compare to what is offered at South African universities will enable the universities to identify how they can better serve the pharmaceutical industry. This can also contribute to the development of an outline to a comprehensive manual or training programme to accommodate the learning needs of a clinical trial biostatistician and may subsequently be used in either a university or business context.

Mathematical Statistics 301 & 302 Third Year

Course Codes: MST 301 and MST 302

Welcome back! We look forward to having you in our third year course.

Course Co-ordinator

Name	Professor Irek Szyszkowski
Room Number	35
Telephone Number	046 603 8348
E-mail Address	i.szyszkowski@ru.ac.za

Please contact your course co-ordinator with any queries or comments concerning the course.

Lecturers: Professor I. Szyszkowski
Professor S. E. Radloff
Mr J. S. Baxter

Regulations

MST 3 is a two-credit third- year course in Mathematical Statistics. It consists of two one-semester courses MST 301 and MST 302 which are held in the 1st and 2nd semesters, respectively. Credit may be obtained in each course separately and an aggregate mark of at least 50% will be deemed to be equivalent to a two-credit course MST 3, provided that a student obtains the sub-minimum of at least 40% in each component.

Prerequisites

Credit in Mathematical Statistics 2 (MST 2) and Mathematics (MAT 1 or MAT 1E) is required before a student may register for MST 301 or MST 302.
A mark of at least 35% in MST 301 is required before a student may register for MST 302.

If a student obtains a pass in a semester course, but fails to gain an aggregate pass for the full course in the following ordinary or supplementary examination, then that student will be required to pass the semester course failed in order to gain the full-credit.

Course Objectives and Content

67 - Computer usage: package specified but not in questionnaire list

MST 3 is an advanced undergraduate course in Mathematical Statistics which covers the theoretical under-pinnings of the major branches of Mathematical Statistics. The course includes a paper in applied theoretical statistics and the use of statistical packages, namely *Statistica* and *BMDP*

Mathematical Statistics 301 & 302
The student will, *inter alia*, know the concepts of:

MST 301

- distribution theory
- normal sampling theory
- multivariate normal disribution
- the general linear model
- non-linear regression
- analysis of variance

43 - Repeated measures/ Multivariate analysis

49 - GLM

48 - Logistic regression

41- ANOVA

MST 302
A selection of topics from:

- limit theorems
- applied stochastic processes
- multivariate statistical procedures
- non-parametric procedures
- sampling techniques
- quality control
- Bayesian inference
- financial statistics
- experimental design

43 - Repeated measures/ Multivariate analysis

44 - Non-parametric

55- Quality control and review

Textbooks and Handouts

It is recommended that students purchase the textbook *Introduction to Mathematical Statistics*, 5th edition by **Hogg and Craig**. The prescribed textbook for the MST 302 course is *An Introduction to Mathematical Finance* by Sheldon M. Ross. Cambridge University Press, 1999.

You will be supplied with notes which cover the contents of the MST 301 and MST 302 courses. The cost of the notes, tutorial material and handouts is incorporated into the course charge of R75,00 per semester.

Students are advised to purchase a copy of: *Statistical Tables*, 3rd edition by **D.J. Stoker.** Second hand copies of this book should be available.

APPENDIX G: TABLES OF THE INDUSTRY SUBGROUP ANALYSIS

Table S.1
Qualifications: Highest qualification and highest statistics qualification

		Contract research organisation		University research/ statistics department		Government research agency	
		n	%	n	%	n	%
Highest qualification	Bachelors degree	2	20.0				
	Honours degree	5	50.0	1	11.1	1	12.5
	Masters degree	2	20.0	4	44.4	4	50.0
	PhD	1	10.0	4	44.4	3	37.5
	Total	10	100.0	9	100.0	8	100.0
Highest statistics qualification	Bachelors degree	2	20.0			1	12.5
	Honours degree	6	60.0	1	11.1	1	12.5
	Masters degree	1	10.0	4	44.4	3	37.5
	PhD	1	10.0	4	44.4	3	37.5
	Total	10	100.0	9	100.0	8	100.0

Table S.2
Previous industries in which respondents worked

		Contract research organisation		University research/ statistics department		Government research agency	
		n	%	n	%	n	%
Previous industry	Pharmaceutical company			1	11.1		
	Contract research organisation	3	30.0	1	11.1	1	12.5
	Government regulatory authority (MCC)					1	12.5
	University research/statistics department	2	20.0	4	44.4	5	62.5
	Government research agency (MRC, Statistics SA)	1	10.0	1	11.1	4	50.0
	Private	1	10.0	1	11.1		
	Other, specify	1	10.0			1	12.5

Note: A respondent may have worked in more than one industry previously

Table S.3
Task experience

Task experience	Contract research organisation		University research/ statistics department		Government research agency	
	n	%	n	%	n	%
Writing clinical development plans					1	12.5
Writing clinical trial protocols	4	40.0	5	55.6	4	50.0
Designing case report forms	5	50.0	4	44.4	3	37.5
Statistical analysis of a clinical trial	10	100.0	8	88.9	8	100.0
Writing clinical trial reports	8	80.0	3	33.3	7	87.5
Sample size calculation	5	50.0	9	100.0	7	87.5
Preparation of randomisation materials	4	40.0	5	55.6	3	37.5
Preparation/review of data management plans	9	90.0	2	22.2	3	37.5
Other	1	10.0				

Note: A respondent may have experience in more than one task

Table S.4
Years of experience and frequency of trial analysis

		Contract research organisation		University research/ statistics department		Government research agency	
		n	%	n	%	n	%
Years of experience	<= 5 years	6	60.0	5	55.6	4	50.0
	6 - 10 years	1	10.0	1	11.1		
	11 - 15 years	2	20.0			1	12.5
	> 15 years	1	10.0	3	33.3	3	37.5
	Total	10	100.0	9	100.0	8	100.0
% time as a CTB	<= 20 %	1	10.0	9	100.0	3	37.5
	21 - 50 %	1	10.0			1	12.5
	51 - 80 %	2	20.0			2	25.0
	> 80 %	6	60.0			2	25.0
	Total	10	100.0	9	100.0	8	100.0
Number of trials a year	<= 3 trials	2	20.0	7	77.8	3	37.5
	4 - 6 trials	4	40.0	1	11.1	2	25.0
	7 - 10 trials	2	20.0	1	11.1	1	12.5
	> 10 trials	2	20.0			2	25.0
	Total	10	100.0	9	100.0	8	100.0

Note: 'Years of experience' refers to experience as a biostatistician and not specifically as a CTB
CTB = Clinical trial biostatistician

Table S.5
Experience in different clinical trial phases

Phase	Contract research organisation		University research/ statistics department		Government research agency	
	n	%	n	%	n	%
Phase I	6	60.0	5	55.6	3	37.5
Phase II	6	60.0	4	44.4	5	62.5
Phase III	8	80.0	4	44.4	4	50.0
Phase IV	6	60.0	1	11.1	4	50.0

Note: A respondent may have worked on clinical trials in more than one phase of development

Table S.6a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: The drug development process and clinical trials

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
Contract research organisation	History and rationale of randomised clinical trial			1	10.0	2	20.0	6	60.0	1	10.0
	Drug development process			2	20.0	6	60.0	2	20.0		
	Conduct of a clinical trial			1	10.0	2	20.0	7	70.0		
	Clinical trial team (the personnel involved in conducting a clinical trial)					2	20.0	8	80.0		
University research/statistics department	History and rationale of randomised clinical trial	2	22.2			1	11.1	5	55.6	1	11.1
	Drug development process	5	55.6	2	22.2			2	22.2		
	Conduct of a clinical trial	1	11.1	1	11.1			7	77.8		
	Clinical trial team (the personnel involved in conducting a clinical trial)	2	22.2	3	33.3			4	44.4		
Government research agency (MRC, Statistics SA)	History and rationale of randomised clinical trial	1	12.5			2	25.0	4	50.0	1	12.5
	Drug development process	3	37.5	1	12.5	3	37.5	1	12.5		
	Conduct of a clinical trial	1	14.3			1	14.3	4	57.1	1	14.3
	Clinical trial team (the personnel involved in conducting a clinical trial)	1	12.5	3	37.5	2	25.0			2	25.0

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.6b
Method of acquiring knowledge/experience
Section: The drug development process and clinical trials

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
Contract research organisation	History and rationale of randomised clinical trial	1	10.0	6	60.0	5	50.0	4	40.0		
	Drug development process			5	50.0	6	60.0	2	20.0		
	Conduct of a clinical trial			6	60.0	6	60.0	3	30.0		
	Clinical trial team (the personnel involved in conducting a clinical trial)			9	90.0	3	30.0	2	20.0		
University research/statistics department	History and rationale of randomised clinical trial	2	22.2	4	44.4			2	22.2		
	Drug development process	1	11.1	3	33.3						
	Conduct of a clinical trial	1	11.1	7	77.8			2	22.2		
	Clinical trial team (the personnel involved in conducting a clinical trial)	1	11.1	6	66.7						
Government research agency (MRC, Statistics SA)	History and rationale of randomised clinical trial	2	25.0	4	50.0	1	12.5	4	50.0	1	12.5
	Drug development process	1	12.5					5	62.5	1	12.5
	Conduct of a clinical trial	3	37.5	3	37.5	1	12.5	6	75.0	1	12.5
	Clinical trial team (the personnel involved in conducting a clinical trial)	1	12.5	4	50.0	1	12.5	4	50.0	1	12.5

Table S.7a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Regulatory requirements and international guidelines

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
Contract research organisation	ICH1 E3 - Structure and content of clinical study reports	2	20.0			1	10.0	5	50.0	2	20.0
	ICH E6 - Good clinical practice	1	10.0			2	20.0	5	50.0	2	20.0
	ICH E9 - Statistical principles for clinical trials					1	10.0	7	70.0	2	20.0
	ICH E10 -Choice of control group in clinical trials	1	10.0	1	10.0	1	10.0	6	60.0	1	10.0
	PSI2 SOP3 guidance documents	4	40.0	3	30.0	1	10.0	2	20.0		
	21 CFR Part 11 - Electronic records and electronic signatures	2	20.0	2	20.0	2	20.0	4	40.0		
	Regulatory submission process	5	50.0	2	20.0	3	30.0				
	Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa	2	20.0	4	40.0	2	20.0	2	20.0		
	Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs)	3	30.0	3	30.0	3	30.0	1	10.0		
University research/statistics department	ICH1 E3 - Structure and content of clinical study reports	6	66.7	1	11.1			2	22.2		
	ICH E6 - Good clinical practice	6	66.7	1	11.1	1	11.1	1	11.1		
	ICH E9 - Statistical principles for clinical trials	3	33.3			1	11.1	4	44.4	1	11.1

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.7a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Regulatory requirements and international guidelines

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
University research/statistics department	ICH E10 -Choice of control group in clinical trials	3	33.3	1	11.1	1	11.1	4	44.4		
	PSI2 SOP3 guidance documents	7	77.8	1	11.1	1	11.1				
	21 CFR Part 11 - Electronic records and electronic signatures	9	100.0								
	Regulatory submission process	7	77.8	2	22.2						
	Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa	8	88.9	1	11.1						
	Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs)	4	44.4	2	22.2			2	22.2	1	11.1
Government research agency (MRC, Statistics SA)	ICH1 E3 - Structure and content of clinical study reports	3	37.5	3	37.5			2	25.0		
	ICH E6 - Good clinical practice	4	50.0	2	25.0	1	12.5	1	12.5		
	ICH E9 - Statistical principles for clinical trials	3	37.5	1	12.5	1	12.5	1	12.5	2	25.0
	ICH E10 -Choice of control group in clinical trials	3	37.5	2	25.0	1	12.5			2	25.0
	PSI2 SOP3 guidance documents	6	75.0			1	12.5	1	12.5		
	21 CFR Part 11 - Electronic records and electronic signatures	7	87.5	1	12.5						

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.7a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Regulatory requirements and international guidelines

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
Government research agency (MRC, Statistics SA)	Regulatory submission process	6	75.0	2	25.0						
	Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa	4	50.0	3	37.5			1	12.5		
	Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs)	3	37.5	2	25.0			2	25.0	1	12.5

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.7b
Method of acquiring knowledge/experience
Section: Regulatory requirements and international guidelines

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
Contract research organisation	ICH1 E3 - Structure and content of clinical study reports			6	60.0	7	70.0	4	40.0	1	10.0
	ICH E6 - Good clinical practice			6	60.0	8	80.0	5	50.0		
	ICH E9 - Statistical principles for clinical trials			7	70.0	8	80.0	6	60.0		
	ICH E10 -Choice of control group in clinical trials	1	10.0	5	50.0	6	60.0	5	50.0		
	PSI2 SOP3 guidance documents			1	10.0	2	20.0	2	20.0	1	10.0
	21 CFR Part 11 - Electronic records and electronic signatures			3	30.0	5	50.0	2	20.0	1	10.0
	Regulatory submission process			3	30.0	1	10.0	1	10.0	1	10.0
	Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa			3	30.0	2	20.0	3	30.0	1	10.0
	Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs)			4	40.0	1	10.0	2	20.0	1	10.0
University research/statistics department	ICH1 E3 - Structure and content of clinical study reports			3	33.3						
	ICH E6 - Good clinical practice	1	11.1	2	22.2						
	ICH E9 - Statistical principles for clinical trials	2	22.2	5	55.6			2	22.2		
	ICH E10 -Choice of control group in clinical trials	1	11.1	3	33.3			2	22.2		
	PSI2 SOP3 guidance documents			1	11.1						

Table S.7b
Method of acquiring knowledge/experience
Section: Regulatory requirements and international guidelines

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
University research/statistics department	Regulatory submission process			1	11.1						
	Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs)	1	11.1	4	44.4	1	11.1	1	11.1		
Government research agency (MRC, Statistics SA)	ICH1 E3 - Structure and content of clinical study reports	1	12.5	1	12.5			3	37.5	1	12.5
	ICH E6 - Good clinical practice	1	12.5					3	37.5	1	12.5
	ICH E9 - Statistical principles for clinical trials	1	12.5	2	25.0			4	50.0	1	12.5
	ICH E10 -Choice of control group in clinical trials	1	12.5	1	12.5			2	25.0	1	12.5
	PSI2 SOP3 guidance documents	1	12.5					1	12.5		
	21 CFR Part 11 - Electronic records and electronic signatures							1	12.5		
	Regulatory submission process							2	25.0		
	Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa							3	37.5	2	25.0
	Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs)			2	25.0			1	12.5	2	25.0

Table S.8a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Clinical trial design

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
Contract research organisation	Types of clinical trials (superiority, equivalence, non-inferiority, etc.)	1	10.0	1	10.0	1	10.0	6	60.0	1	10.0
	Clinical trial designs (parallel, cross-over, dose-response studies, etc)					2	20.0	5	50.0	3	30.0
	Types of outcome variables (composite variables, etc)	2	20.0					8	80.0		
	Sample size calculation	1	10.0			5	50.0	3	30.0	1	10.0
	Statistical considerations for protocol review (including protocol amendments)	1	10.0					9	90.0		
	Randomisation and blinding (generating randomisation plans and preparing related documents)			1	10.0	4	40.0	3	30.0	2	20.0
	Statistical considerations for CRF design	2	20.0			2	20.0	4	40.0	2	20.0
	Statistical considerations for interim analyses			1	10.0	2	20.0	7	70.0		
	Statistical considerations for Data Safety Monitoring Boards1	4	40.0			1	10.0	5	50.0		
	Avoiding bias in clinical trials	1	10.0			2	20.0	7	70.0		
University research/statistics department	Types of clinical trials (superiority, equivalence, non-inferiority, etc.)	2	22.2	3	33.3			4	44.4		
	Clinical trial designs (parallel, cross-over, dose-response studies, etc)	1	11.1	1	11.1	1	11.1	5	55.6	1	11.1

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.8a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Clinical trial design

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
University research/statistics department	Types of outcome variables (composite variables, etc)	1	11.1	1	11.1			6	66.7	1	11.1
	Sample size calculation	1	11.1			1	11.1	5	55.6	2	22.2
	Statistical considerations for protocol review (including protocol amendments)	1	11.1	2	22.2	1	11.1	3	33.3	2	22.2
	Randomisation and blinding (generating randomisation plans and preparing related documents)	1	11.1	1	11.1	2	22.2	4	44.4	1	11.1
	Statistical considerations for CRF design	3	33.3			2	22.2	2	22.2	2	22.2
	Statistical considerations for interim analyses	5	55.6	1	11.1	1	11.1	2	22.2		
	Statistical considerations for Data Safety Monitoring Boards1	7	77.8			1	11.1	1	11.1		
	Avoiding bias in clinical trials	1	11.1	2	22.2	1	11.1	4	44.4	1	11.1
Government research agency (MRC, Statistics SA)	Types of clinical trials (superiority, equivalence, non-inferiority, etc.)	1	12.5			2	25.0	4	50.0	1	12.5
	Clinical trial designs (parallel, cross-over, dose-response studies, etc)			1	12.5	1	12.5	4	50.0	2	25.0
	Types of outcome variables (composite variables, etc)			1	12.5	2	25.0	3	37.5	2	25.0
	Sample size calculation			1	12.5	2	25.0	3	37.5	2	25.0

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.8a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Clinical trial design

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
Government research agency (MRC, Statistics SA)	Statistical considerations for protocol review (including protocol amendments)	3	37.5	1	12.5	1	12.5	1	12.5	2	25.0
	Randomisation and blinding (generating randomisation plans and preparing related documents)	1	12.5	1	12.5	1	12.5	3	37.5	2	25.0
	Statistical considerations for CRF design	2	25.0	3	37.5	1	12.5			2	25.0
	Statistical considerations for interim analyses			2	25.0	2	25.0	1	12.5	3	37.5
	Statistical considerations for Data Safety Monitoring Boards1	4	50.0			1	12.5	1	12.5	2	25.0
	Avoiding bias in clinical trials			2	28.6	2	28.6	1	14.3	2	28.6

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.8b
Method of acquiring knowledge/experience
Section: Clinical trial design

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
Contract research organisation	Types of clinical trials (superiority, equivalence, non-inferiority, etc.)	2	20.0	6	60.0	7	70.0	4	40.0		
	Clinical trial designs (parallel, cross-over, dose-response studies, etc)	4	40.0	6	60.0	7	70.0	5	50.0		
	Types of outcome variables (composite variables, etc)	1	10.0	7	70.0	2	20.0	2	20.0		
	Sample size calculation	5	50.0	5	50.0	1	10.0	4	40.0		
	Statistical considerations for protocol review (including protocol amendments)			8	80.0	2	20.0	2	20.0		
	Randomisation and blinding (generating randomisation plans and preparing related documents)	3	30.0	4	40.0	6	60.0	2	20.0		
	Statistical considerations for CRF design	1	10.0	7	70.0	3	30.0	2	20.0		
	Statistical considerations for interim analyses			8	80.0	5	50.0	2	20.0		
	Statistical considerations for Data Safety Monitoring Boards1			5	50.0	2	20.0	2	20.0		
	Avoiding bias in clinical trials	4	40.0	6	60.0	5	50.0	4	40.0		
University research/statistics department	Types of clinical trials (superiority, equivalence, non-inferiority, etc.)	1	11.1	7	77.8			2	22.2		
	Clinical trial designs (parallel, cross-over, dose-response studies, etc)	1	11.1	7	77.8			4	44.4		
	Types of outcome variables (composite variables, etc)	1	11.1	6	66.7			4	44.4		

Table S.8b
Method of acquiring knowledge/experience
Section: Clinical trial design

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
University research/statistics department	Sample size calculation	6	66.7	6	66.7			4	44.4		
	Statistical considerations for protocol review (including protocol amendments)	1	11.1	6	66.7			2	22.2		
	Randomisation and blinding (generating randomisation plans and preparing related documents)	2	22.2	5	55.6			3	33.3		
	Statistical considerations for CRF design	2	22.2	3	33.3			3	33.3		
	Statistical considerations for interim analyses	1	11.1	2	22.2			1	11.1		
	Statistical considerations for Data Safety Monitoring Boards1	1	11.1	1	11.1			1	11.1		
	Avoiding bias in clinical trials	1	11.1	6	66.7			4	44.4		
Government research agency (MRC, Statistics SA)	Types of clinical trials (superiority, equivalence, non-inferiority, etc.)	1	12.5	3	37.5			6	75.0	1	12.5
	Clinical trial designs (parallel, cross-over, dose-response studies, etc)	3	37.5	3	37.5			7	87.5	1	12.5
	Types of outcome variables (composite variables, etc)	2	25.0	3	37.5	1	12.5	7	87.5	1	12.5
	Sample size calculation	3	37.5	3	37.5	1	12.5	7	87.5	1	12.5
	Statistical considerations for protocol review (including protocol amendments)	1	12.5	3	37.5			2	25.0		

Table S.8b
Method of acquiring knowledge/experience
Section: Clinical trial design

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
Government research agency (MRC, Statistics SA)	Randomisation and blinding (generating randomisation plans and preparing related documents)	3	37.5	2	25.0			6	75.0	1	12.5
	Statistical considerations for CRF design	1	12.5	2	25.0			4	50.0		
	Statistical considerations for interim analyses	2	25.0	3	37.5	1	12.5	6	75.0	1	12.5
	Statistical considerations for Data Safety Monitoring Boards1	1	12.5	1	12.5	1	12.5	3	37.5	1	12.5
	Avoiding bias in clinical trials	3	37.5	3	37.5	2	25.0	5	62.5	1	12.5

Table S.9a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Data management

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
Contract research organisation	Data management for clinical trials			2	20.0	2	20.0	5	50.0	1	10.0
	Biostatistical input into data management processes							9	90.0	1	10.0
	Conducting the statistical review of a database			1	10.0	2	20.0	6	60.0	1	10.0
University research/statistics department	Data management for clinical trials	2	22.2	1	11.1			6	66.7		
	Biostatistical input into data management processes	2	22.2	1	11.1			6	66.7		
	Conducting the statistical review of a database	3	33.3					4	44.4	2	22.2
Government research agency (MRC, Statistics SA)	Data management for clinical trials			1	12.5	2	25.0	3	37.5	2	25.0
	Biostatistical input into data management processes			1	12.5	2	25.0	3	37.5	2	25.0
	Conducting the statistical review of a database	3	37.5	2	25.0	1	12.5			2	25.0

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.9b
Method of acquiring knowledge/experience
Section: Data management

Subgroup	Topic	University degree		On-the-job training		Formal in-house training		Self-study /reading		Other training course(s)	
		n	%	n	%	n	%	n	%	n	%
Contract research organisation	Data management for clinical trials	1	10.0	7	70.0	7	70.0	2	20.0		
	Biostatistical input into data management processes			8	80.0	5	50.0	4	40.0		
	Conducting the statistical review of a database			8	80.0	4	40.0	2	20.0		
University research/statistics department	Data management for clinical trials	1	11.1	6	66.7			1	11.1		
	Biostatistical input into data management processes	1	11.1	6	66.7			2	22.2		
	Conducting the statistical review of a database	1	11.1	5	55.6			2	22.2		
Government research agency (MRC, Statistics SA)	Data management for clinical trials	1	12.5	5	62.5	3	37.5	5	62.5		
	Biostatistical input into data management processes	1	12.5	5	62.5	3	37.5	4	50.0		
	Conducting the statistical review of a database			2	25.0	1	12.5	2	25.0		

Table S.10a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Statistical analysis considerations

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
Contract research organisation	Writing statistical analysis plans							5	50.0	5	50.0
	Writing derived dataset specifications	1	10.0			2	20.0	7	70.0		
	Identifying analysis populations							7	70.0	3	30.0
	Conducting a blind review of data							7	70.0	3	30.0
	Presentation/analysis of demographic and background data							5	50.0	5	50.0
	Presentation/analysis of laboratory data							8	80.0	2	20.0
	Presentation/analysis of adverse events							8	80.0	2	20.0
	Presentation/analysis of concomitant illnesses and medication, medical history and previous medications							8	80.0	2	20.0
	Data analysis considerations (covariates, interactions, etc)	1	10.0			1	10.0	6	60.0	2	20.0
	International medical coding dictionaries							10	100.0		
	Programming considerations and documentation (Good programming practices)							9	90.0	1	10.0
	Pharmacokinetics and Pharmacodynamics	1	10.0	1	10.0	3	30.0	4	40.0	1	10.0
	Bioequivalence studies	2	20.0	2	20.0	2	20.0	2	20.0	2	20.0
University research/statistics department	Writing statistical analysis plans	3	33.3	1	11.1			4	44.4	1	11.1
	Writing derived dataset specifications	5	55.6	3	33.3			1	11.1		

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.10a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Statistical analysis considerations

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
University research/statistics department	Identifying analysis populations	4	44.4					5	55.6		
	Conducting a blind review of data	6	66.7	1	11.1			2	22.2		
	Presentation/analysis of demographic and background data	2	22.2					5	55.6	2	22.2
	Presentation/analysis of laboratory data	2	22.2	1	11.1			5	55.6	1	11.1
	Presentation/analysis of adverse events	4	44.4					5	55.6		
	Presentation/analysis of concomitant illnesses and medication, medical history and previous medications	4	44.4					5	55.6		
	Data analysis considerations (covariates, interactions, etc)	2	22.2					6	66.7	1	11.1
	International medical coding dictionaries	6	66.7	1	11.1			2	22.2		
	Programming considerations and documentation (Good programming practices)	3	33.3	1	11.1			5	55.6		
	Pharmacokinetics and Pharmacodynamics	5	55.6	1	11.1			3	33.3		
	Bioequivalence studies	4	44.4	2	22.2			2	22.2	1	11.1
Government research agency (MRC, Statistics SA)	Writing statistical analysis plans			2	25.0	2	25.0	2	25.0	2	25.0
	Writing derived dataset specifications	3	37.5	3	37.5	1	12.5			1	12.5
	Identifying analysis populations	2	25.0	2	25.0	1	12.5	2	25.0	1	12.5

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.10a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Statistical analysis considerations

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
Government research agency (MRC, Statistics SA)	Conducting a blind review of data	3	37.5	3	37.5			2	25.0		
	Presentation/analysis of demographic and background data							5	62.5	3	37.5
	Presentation/analysis of laboratory data			1	12.5			6	75.0	1	12.5
	Presentation/analysis of adverse events	1	12.5	3	37.5			3	37.5	1	12.5
	Presentation/analysis of concomitant illnesses and medication, medical history and previous medications	1	12.5	2	25.0			4	50.0	1	12.5
	Data analysis considerations (covariates, interactions, etc)							5	62.5	3	37.5
	International medical coding dictionaries	4	50.0	4	50.0						
	Programming considerations and documentation (Good programming practices)	1	12.5	2	25.0			3	37.5	2	25.0
	Pharmacokinetics and Pharmacodynamics	4	50.0			2	25.0	2	25.0		
	Bioequivalence studies	3	37.5	1	12.5	1	12.5	2	25.0	1	12.5

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.10b
Method of acquiring knowledge/experience
Section: Statistical analysis considerations

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
Contract research organisation	Writing statistical analysis plans			9	90.0	7	70.0	4	40.0		
	Writing derived dataset specifications			7	70.0	4	40.0	2	20.0		
	Identifying analysis populations			9	90.0	8	80.0	4	40.0		
	Conducting a blind review of data			9	90.0	7	70.0	3	30.0		
	Presentation/analysis of demographic and background data	2	20.0	9	90.0	6	60.0	3	30.0		
	Presentation/analysis of laboratory data			9	90.0	6	60.0	2	20.0		
	Presentation/analysis of adverse events			9	90.0	5	50.0	2	20.0		
	Presentation/analysis of concomitant illnesses and medication, medical history and previous medications			9	90.0	5	50.0	2	20.0		
	Data analysis considerations (covariates, interactions, etc)	3	30.0	7	70.0	3	30.0	2	20.0		
	International medical coding dictionaries			9	90.0	8	80.0	3	30.0		
	Programming considerations and documentation (Good programming practices)	1	10.0	8	80.0	7	70.0	4	40.0		
	Pharmacokinetics and Pharmacodynamics			4	40.0	7	70.0	2	20.0		
	Bioequivalence studies			3	30.0	5	50.0	3	30.0		
University research/statistics department	Writing statistical analysis plans	1	11.1	6	66.7			1	11.1		
	Writing derived dataset specifications	1	11.1	2	22.2						
	Identifying analysis populations	1	11.1	4	44.4			1	11.1		
	Conducting a blind review of data	1	11.1	1	11.1			1	11.1		

Table S.10b
Method of acquiring knowledge/experience
Section: Statistical analysis considerations

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
University research/statistics department	Presentation/analysis of demographic and background data	3	33.3	6	66.7			2	22.2		
	Presentation/analysis of laboratory data	1	11.1	6	66.7			2	22.2		
	Presentation/analysis of adverse events	1	11.1	5	55.6						
	Presentation/analysis of concomitant illnesses and medication, medical history and previous medications	1	11.1	5	55.6						
	Data analysis considerations (covariates, interactions, etc)	3	33.3	6	66.7			2	22.2		
	International medical coding dictionaries	1	11.1	2	22.2						
	Programming considerations and documentation (Good programming practices)	1	11.1	5	55.6			1	11.1		
	Pharmacokinetics and Pharmacodynamics	1	11.1	4	44.4	1	11.1	2	22.2		
	Bioequivalence studies	1	11.1	4	44.4	1	11.1	2	22.2		
Government research agency (MRC, Statistics SA)	Writing statistical analysis plans	3	37.5	4	50.0	1	12.5	5	62.5		
	Writing derived dataset specifications			2	25.0			1	12.5		
	Identifying analysis populations	1	12.5	3	37.5	1	12.5	3	37.5		
	Conducting a blind review of data			2	25.0	1	12.5	2	25.0		
	Presentation/analysis of demographic and background data	2	25.0	4	50.0	1	12.5	5	62.5		
	Presentation/analysis of laboratory data	2	25.0	4	50.0			5	62.5		
	Presentation/analysis of adverse events	2	25.0	4	50.0			3	37.5		

Table S.10b
Method of acquiring knowledge/experience
Section: Statistical analysis considerations

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
Government research agency (MRC, Statistics SA)	Presentation/analysis of concomitant illnesses and medication, medical history and previous medications	1	12.5	3	37.5			4	50.0		
	Data analysis considerations (covariates, interactions, etc)	5	62.5	4	50.0	1	12.5	6	75.0		
	International medical coding dictionaries			1	12.5			2	25.0		
	Programming considerations and documentation (Good programming practices)	1	12.5	4	50.0	1	12.5	4	50.0		
	Pharmacokinetics and Pharmacodynamics	2	25.0					3	37.5		
	Bioequivalence studies	3	37.5	1	12.5			3	37.5		

Table S.11a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Statistical methods

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
Contract research organisation	ANOVA/ANCOVA			1	10.0	1	10.0	5	50.0	3	30.0
	Linear regression	1	10.0			2	20.0	7	70.0		
	Repeated measures/Multivariate analysis	1	10.0			3	30.0	6	60.0		
	Non-parametric methods	1	10.0			2	20.0	7	70.0		
	Contingency tables					2	20.0	6	60.0	2	20.0
	Risk ratios / odds ratios / Mantel-Haenzel method	1	10.0			1	10.0	6	60.0	2	20.0
	Logistic regression	1	10.0	1	10.0	2	20.0	6	60.0		
	Generalised linear models			1	10.0	3	30.0	5	50.0	1	10.0
	Exact tests			1	10.0	2	20.0	5	50.0	2	20.0
	Analysis of survival data (incl. Cox regression, Kaplan-Meier estimates)	2	20.0	1	10.0	1	10.0	5	50.0	1	10.0
University research/statistics department	ANOVA/ANCOVA					1	11.1	2	22.2	6	66.7
	Linear regression			1	11.1	2	22.2	1	11.1	5	55.6
	Repeated measures/Multivariate analysis					2	22.2	3	33.3	4	44.4
	Non-parametric methods					1	11.1	3	33.3	5	55.6
	Contingency tables	1	11.1					2	22.2	6	66.7
	Risk ratios / odds ratios / Mantel-Haenzel method					3	33.3	2	22.2	4	44.4
	Logistic regression	1	11.1			2	22.2	3	33.3	3	33.3

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.11a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Statistical methods

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
University research/statistics department	Generalised linear models	1	11.1					5	55.6	3	33.3
	Exact tests					1	11.1	4	44.4	4	44.4
	Analysis of survival data (incl. Cox regression, Kaplan-Meier estimates)	1	11.1			2	22.2	5	55.6	1	11.1
Government research agency (MRC, Statistics SA)	ANOVA/ANCOVA							3	37.5	5	62.5
	Linear regression							3	37.5	5	62.5
	Repeated measures/Multivariate analysis							3	37.5	5	62.5
	Non-parametric methods							4	50.0	4	50.0
	Contingency tables							3	37.5	5	62.5
	Risk ratios / odds ratios / Mantel-Haenzel method							4	50.0	4	50.0
	Logistic regression							3	37.5	5	62.5
	Generalised linear models							3	37.5	5	62.5
	Exact tests			1	12.5			3	37.5	4	50.0
	Analysis of survival data (incl. Cox regression, Kaplan-Meier estimates)			1	12.5			2	25.0	5	62.5

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.11b
Method of acquiring knowledge/experience
Section: Statistical methods

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
Contract research organisation	ANOVA/ANCOVA	8	80.0	7	70.0	1	10.0	4	40.0		
	Linear regression	7	70.0	3	30.0	1	10.0	4	40.0		
	Repeated measures/Multivariate analysis	7	70.0	5	50.0	1	10.0	3	30.0		
	Non-parametric methods	6	60.0	5	50.0	1	10.0	4	40.0		
	Contingency tables	7	70.0	8	80.0	2	20.0	3	30.0		
	Risk ratios / odds ratios / Mantel-Haenzel method	5	50.0	8	80.0	1	10.0	2	20.0		
	Logistic regression	5	50.0	4	40.0	1	10.0	2	20.0		
	Generalised linear models	8	80.0	5	50.0	1	10.0	2	20.0		
	Exact tests	6	60.0	7	70.0	1	10.0	3	30.0		
	Analysis of survival data (incl. Cox regression, Kaplan-Meier estimates)			6	60.0	1	10.0	4	40.0		
University research/statistics department	ANOVA/ANCOVA	9	100.0	5	55.6			3	33.3		
	Linear regression	9	100.0	5	55.6			2	22.2		
	Repeated measures/Multivariate analysis	7	77.8	5	55.6			4	44.4		
	Non-parametric methods	7	77.8	7	77.8			5	55.6		
	Contingency tables	7	77.8	6	66.7			5	55.6		
	Risk ratios / odds ratios / Mantel-Haenzel method	5	55.6	4	44.4			5	55.6		
	Logistic regression	3	33.3	4	44.4			4	44.4	1	11.1
	Generalised linear models	6	66.7	6	66.7			4	44.4		
	Exact tests	6	66.7	6	66.7			3	33.3		

Table S.11b
Method of acquiring knowledge/experience
Section: Statistical methods

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
University research/statistics department	Analysis of survival data (incl. Cox regression, Kaplan-Meier estimates)	4	44.4	4	44.4			3	33.3		
Government research agency (MRC, Statistics SA)	ANOVA/ANCOVA	7	87.5	5	62.5	1	12.5	5	62.5	1	12.5
	Linear regression	6	75.0	5	62.5	1	12.5	5	62.5	1	12.5
	Repeated measures/Multivariate analysis	5	62.5	5	62.5	1	12.5	5	62.5	1	12.5
	Non-parametric methods	7	87.5	5	62.5			4	50.0		
	Contingency tables	7	87.5	5	62.5	1	12.5	5	62.5	1	12.5
	Risk ratios / odds ratios / Mantel-Haenzel method	5	62.5	5	62.5			6	75.0	1	12.5
	Logistic regression	5	62.5	5	62.5	1	12.5	6	75.0	1	12.5
	Generalised linear models	4	50.0	5	62.5	1	12.5	6	75.0	1	12.5
	Exact tests	5	62.5	5	62.5	1	12.5	5	62.5		
	Analysis of survival data (incl. Cox regression, Kaplan-Meier estimates)	5	62.5	5	62.5	1	12.5	6	75.0	1	12.5

Table S.12a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Reporting

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
Contract research organisation	Medical writing (scientific writing) style and conventions	1	10.0	2	20.0			5	50.0	2	20.0
	Writing/reviewing publications	2	20.0	2	20.0			6	60.0		
	Writing/reviewing clinical study report	1	10.0	1	10.0			6	60.0	2	20.0
University research/statistics department	Medical writing (scientific writing) style and conventions	2	22.2	3	33.3			3	33.3	1	11.1
	Writing/reviewing publications	1	11.1	2	22.2	1	11.1	1	11.1	4	44.4
	Writing/reviewing clinical study report	2	22.2	3	33.3			3	33.3	1	11.1
Government research agency (MRC, Statistics SA)	Medical writing (scientific writing) style and conventions			2	25.0			3	37.5	3	37.5
	Writing/reviewing publications	1	12.5	2	25.0			3	37.5	2	25.0
	Writing/reviewing clinical study report	1	12.5	2	25.0			4	50.0	1	12.5

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.12b
Method of acquiring knowledge/experience
Section: Reporting

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
Contract research organisation	Medical writing (scientific writing) style and conventions			8	80.0	3	30.0	2	20.0		
	Writing/reviewing publications	1	10.0	5	50.0	3	30.0	3	30.0		
	Writing/reviewing clinical study report			7	70.0	6	60.0	2	20.0		
University research/statistics department	Medical writing (scientific writing) style and conventions	1	11.1	7	77.8						
	Writing/reviewing publications	1	11.1	6	66.7			2	22.2		
	Writing/reviewing clinical study report	1	11.1	7	77.8						
Government research agency (MRC, Statistics SA)	Medical writing (scientific writing) style and conventions	1	12.5	3	37.5	2	25.0	5	62.5		
	Writing/reviewing publications	1	12.5	4	50.0	1	12.5	4	50.0		
	Writing/reviewing clinical study report	1	12.5	3	37.5	1	12.5	4	50.0	1	12.5

Table S.13a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Quality control and documentation

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
Contract research organisation	Quality control and review processes	1	10.0					8	80.0	1	10.0
	Maintaining project documentation (including version control etc)							9	90.0	1	10.0
	Paper and electronic archiving			2	20.0			8	80.0		
University research/statistics department	Quality control and review processes	3	33.3	2	22.2	2	22.2	2	22.2		
	Maintaining project documentation (including version control etc)	4	44.4	4	44.4	1	11.1				
	Paper and electronic archiving	3	33.3	2	22.2	1	11.1	3	33.3		
Government research agency (MRC, Statistics SA)	Quality control and review processes	3	37.5	2	25.0	1	12.5	2	25.0		
	Maintaining project documentation (including version control etc)	2	25.0	2	25.0	1	12.5	3	37.5		
	Paper and electronic archiving	4	50.0	1	12.5			3	37.5		

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.13b
Method of acquiring knowledge/experience
Section: Quality control and documentation

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
Contract research organisation	Quality control and review processes			8	80.0	4	40.0	1	10.0		
	Maintaining project documentation (including version control etc)			9	90.0	4	40.0	2	20.0		
	Paper and electronic archiving			9	90.0	3	30.0	1	10.0		
University research/statistics department	Quality control and review processes	2	22.2	2	22.2			1	11.1		
	Maintaining project documentation (including version control etc)	1	11.1	3	33.3						
	Paper and electronic archiving	1	11.1	4	44.4			1	11.1		
Government research agency (MRC, Statistics SA)	Quality control and review processes	1	12.5	2	25.0			2	25.0		
	Maintaining project documentation (including version control etc)	1	12.5	3	37.5			2	25.0		
	Paper and electronic archiving			3	37.5	1	12.5	1	12.5		

Table S.14a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Computer skills/packages

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
Contract research organisation	MS Word							4	40.0	6	60.0
	MS Excel							6	60.0	4	40.0
	MS PowerPoint							9	90.0	1	10.0
	NQuery	7	70.0	2	20.0	1	10.0				
	StatXact	6	60.0	2	20.0	1	10.0	1	10.0		
	WinNonLin	7	70.0	1	10.0			1	10.0	1	10.0
	SAS							8	80.0	2	20.0
	CIA	7	70.0	2	20.0			1	10.0		
University research/statistics department	MS Word							5	55.6	4	44.4
	MS Excel							4	44.4	5	55.6
	MS PowerPoint	1	11.1	2	22.2			4	44.4	2	22.2
	NQuery	9	100.0								
	StatXact	7	77.8					1	11.1	1	11.1
	WinNonLin	9	100.0								
	SAS			1	11.1			3	33.3	5	55.6
	CIA	5	55.6					2	22.2	2	22.2
Government research agency (MRC, Statistics SA)	MS Word							3	37.5	5	62.5

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.14a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Computer skills/packages

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
Government research agency (MRC, Statistics SA)	MS Excel							4	50.0	4	50.0
	MS PowerPoint			1	12.5			3	37.5	4	50.0
	NQuery	4	50.0	1	12.5			2	25.0	1	12.5
	StatXact	5	62.5	1	12.5			1	12.5	1	12.5
	WinNonLin	8	100.0								
	SAS							3	37.5	5	62.5
	CIA	7	87.5					1	12.5		

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.14b
Method of acquiring knowledge/experience
Section: Computer skills/packages

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
Contract research organisation	MS Word	6	60.0	9	90.0	3	30.0	6	60.0	1	10.0
	MS Excel	6	60.0	8	80.0	2	20.0	6	60.0		
	MS PowerPoint	3	30.0	6	60.0			5	50.0	1	10.0
	NQuery			1	10.0			1	10.0		
	StatXact			2	20.0			1	10.0		
	WinNonLin			1	10.0			1	10.0		
	SAS	2	20.0	9	90.0	6	60.0	8	80.0	2	20.0
	CIA			1	10.0			1	10.0		
University research/statistics department	MS Word	1	11.1	4	44.4			7	77.8		
	MS Excel	1	11.1	4	44.4			7	77.8		
	MS PowerPoint			2	22.2			6	66.7		
	StatXact	1	11.1	1	11.1	1	11.1	1	11.1		
	SAS	1	11.1	8	88.9	2	22.2	4	44.4		
	CIA			3	33.3			3	33.3		
Government research agency (MRC, Statistics SA)	MS Word	1	12.5	3	37.5	1	12.5	4	50.0		
	MS Excel	1	12.5	3	37.5	1	12.5	4	50.0		
	MS PowerPoint			3	37.5	1	12.5	4	50.0		
	NQuery			2	25.0	1	12.5	2	25.0		
	StatXact	1	12.5			1	12.5	1	12.5		

Table S.14b
Method of acquiring knowledge/experience
Section: Computer skills/packages

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
Government research agency (MRC, Statistics SA)	SAS	3	37.5	4	50.0	2	25.0	5	62.5	1	12.5
	CIA							1	12.5		

Table S.15a
Knowledge/Experience in topics applicable to a clinical trial biostatistician
Section: Other appropriate topics

Subgroup	Topic	No knowledge/ experience n	%	Little knowledge/ experience n	%	Theoretical knowledge only n	%	Working knowledge n	%	Extensive experience n	%
Contract research organisation	ClinTrial: Design of a database							1	100.0		
	Design and maintainence of quality assessment database									1	100.0
	International Standards Organisation (ISO 9001-2000)							1	100.0		
University research/statistics department	Fortran							1	100.0		
Government research agency (MRC, Statistics SA)	Cluster randomised clinical trials									1	100.0
	Consent statement									1	100.0
	Cochrane collaboration									1	100.0
	Meta-analysis of randomised clinical trials									1	100.0
	Pragmatic randomised clinical trials									1	100.0
	Minimisation							1	100.0		
	SYSTAT									1	100.0
	SPSS									1	100.0
	Epidemiology							1	50.0	1	50.0
	Bayesian analysis									1	100.0

Note: If a respondent did not indicate their level of knowledge/experience this omission was taken as 'No knowledge/experience' except for 'Other appropriate topics' where this was taken as missing.

Table S.15b
Method of acquiring knowledge/experience
Section: Other appropriate topics

Subgroup	Topic	University degree n	%	On-the-job training n	%	Formal in-house training n	%	Self-study /reading n	%	Other training course(s) n	%
Contract research organisation	ClinTrial: Design of a database			1	10.0	1	10.0	1	10.0		
	Design and maintainence of quality assessment database							1	100.0		
	International Standards Organisation (ISO 9001-2000)					1	100.0	1	100.0		
University research/statistics department	Fortran	1	100.0	1	100.0			1	100.0		
Government research agency (MRC, Statistics SA)	Cluster randomised clinical trials							1	33.3		
	Consent statement							1	33.3		
	Cochrane collaboration							1	33.3		
	Meta-analysis of randomised clinical trials							1	33.3		
	Pragmatic randomised clinical trials							1	33.3		
	Minimisation							1	33.3		
	SYSTAT			1	33.3						
	SPSS			1	33.3	1	33.3				
	Epidemiology	1	33.3	1	33.3	1	33.3	1	33.3		
	Bayesian analysis	1	33.3					1	33.3		