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Malesela, Ledile Mmabatho Hendricca

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AN ANALYSIS OF ETHICAL ISSUES ARISING IN THE CURRENT GOVERNANCE OF CLINICAL TRIALS FOR COMPLEMENTARY MEDICINES IN SOUTH AFRICA: LOOKING TOWARDS THE FUTURE

Ledile Mmabatho Hendricca Malesela
STUDENT NO: 507886

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Medicine in the field of Bioethics and Health Law

Johannesburg, October 2017

Supervisor: Dr Louise Bezuidenhout BA, BSc (Hons), MA, PhD (Cape Town), PhD (Exeter)

DECLARATION

I, Ledile Mmabatho Hendricca Malesela declare that this research report 'An analysis of ethical issues arising in the current governance of clinical trials for Complementary Medicines in South Africa: Looking towards the future is my own work. It is being submitted for the degree of MSC Med (Bioethics and Health Law) in the University of the Witwatersrand, Johannesburg. I have followed the required conventions in referencing the thoughts and ideas of others. It has not been submitted before for any degree or examination at this or any other University.

LMH Malesela **Date**

DEDICATION

This research report is dedicated to my parents (Mr Nkholoane Maxwell and Reverend Raphahle Albertina Malesela), my handsome son Tshegofatso Keabetswe Nkholoane Malesela and my siblings (Lesetja Freddy Malesela, Mpshebosego Ngwato Malesela and Mosima Monicca Malesela), for their endless love, support and encouragement during moments of despair and discouragement.

ABSTRACT

The WHO (World Health Organization) estimates that 80% of the world's population use Complementary Medicines (CMs) as their primary source of healthcare. Similar figures have been reported in the South African population (Siegfried &Hughes, 2012: 2). The high numbers of CMs users in South Africa (S.A) raises considerable questions about how best to safeguard patient and population health, and what responsibilities the government has towards regulation of medicines and practitioners. This, in turn raises the issues of how best to assess CMs – and thus whether clinical trials are an appropriate method of assessment.

The considerable difference between the systems of CMs and Allopathic Medicines raises concerns when applying clinical trial practices to CMs assessment. Clinical trials, as the gold standard for assessing medical efficacy in Allopathic Medicine, reflect specific interpretations of medicine and health. It has been noted that the key practices in clinical trials for Allopathic Medicines such as randomisation, blinding and placebo can be very difficult to adhere to when investigating CMs. Thus, the use of clinical trials to assess CMs raises a range of different concerns, from the validity of the trials to the potential harm to trial participants.

There is considerable interest in S.A to improve legislation governing the widespread use of CMs. Nonetheless, the development of legislative oversight requires further consideration. In this research report, I will be critically interrogating the current legislation in S.A from an ethical perspective to identify areas requiring further attention. These issues include threats to participant well-being, threats to the efficacy of the trials, and long-term threats caused by potentially incomplete trial data. My research considers ways in which these ethical considerations can be ameliorated by directed changes to the legislation. This research report will conclude by offering a range of recommendations for improvement to the governance of CMs clinical trials in S.A. The recommendations are made to the relevant departments which are making decisions with regards to clinical trials in S.A.

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ABBREVIATIONS AND ACRONYMS

ARGCM.....Australian Regulatory Guidelines for Complementary Medicines

ATM.....African Traditional Medicine

CM.....Complementary Medicine

CSIR.....Council for Scientific and Industrial Research

DSMB.....Data and Safety Monitoring Boards

HREC.....Human Research Ethics Committee

ICH GCP.....International Conference on Harmonization Good Clinical Practice

MCC.....Medicines Control Council

MRC.....Medical Research Council

NDOH.....National Department of Health

RCT.....Randomized Clinical Trial

REC.....Research Ethics Committee

S.A.....South Africa

SAGCP.....South African Good Clinical Practice

TCM.....Traditional Chinese Medicine

TM.....Traditional Medicine

WHO.....World Health Organization

CHAPTER 1-DIFFERING APPROACHES TO HEALTH AND WELL BEING: COMPLEMENTARY MEDICINES AND ALLOPATHIC MEDICINES

This chapter outlines the differences between Complementary Medicines (CMs) and Allopathic Medicines using existing literature. In order to discuss legislation and oversight of CMs it is first important to understand the terminology, what are the problems and why do we need to discuss it. In this chapter, the definition of a Medicine according to the Medicines Act 101 of 1965 (1965:3) which means "any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in- (a) the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man; or (b) restoring, correcting or modifying any somatic or psychic or organic function in man, and includes any veterinary medicine" is used.

The types of ethical issues that this research report was focusing on were threats to participant well-being, threats to the efficacy of the trials and long-term threats caused by potentially incomplete trial data. The research looked at issues of informed consent, autonomy, justice, beneficence and non-maleficence. These issues are from a policy and governance perspective and they do not necessarily delving in to patient-related issues or intellectual property/ownership issues.

1.1 INTRODUCTION

In this section, the definitions of Allopathic Medicines and CMs will be provided. The differences between the two systems of healthcare provision will also be examined. While the uses of Allopathic medicines are exponentially increasing, CMs[1] remain widely used around the world as a primary means of health care (Boon et al., 2006:21). People use CMs due to a number of reasons such as their cultural use, historical use, availability and the fact that there are no options for them to effectively engage with allopathic treatments (Witkowksi, 2002:456).

[1] For the purpose of this research report, the word 'Complementary Medicine' will be used instead of 'Non-Allopathic Medicine'.

Recognizing the differences between these two systems of health provision is key to understanding the issues raised in this research report.

1.2 UNDERSTANDING THE TERMINOLOGY

1.2.1 ALLOPATHIC MEDICINE

Allopathic Medicine[2] is increasingly the dominant system of health provision in western culture, and can be said to reflect cultural attitudes to health and disease. Indeed, Allopathic Medicines rely on interpretations of disease and illness related to physiological causes, and thus aim to restore healing to the physical body and alleviate physical suffering by addressing the biological cause of the illness. Allopathic Medicines are characterized by the testing, measurement and scientific observation of an illness (Gilbert et al., 1996:50), and have come to be largely synonymous with the notion of a scientific approach or method. This may be taken to refer to the practice of "accurate observations, arranging the facts in some orderly manner to determine relationships and drawing conclusions" (Stiles, 1942:13).

As defined by the Medicines Act (1965:3), Allopathic Medicines refer to "any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in a) The diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man; or restoring, correcting or modifying any somatic or psychic or organic function in man, and includes any veterinary medicine". In this way, it may be said that Allopathic Medicines focus on identifying active compounds to treat somatic causes of diseases.

What is evident from this definition is the clear link between the active compound and the disease/symptom it is designed to treat. Understanding Allopathic Medicines also requires recognition of the increasingly standardized manner in which these active compounds are identified, developed and evaluated. This

[2] Also known as Western, Conventional, Orthodox and Mainstream.

involves highly routinized laboratory investigation to isolate active compounds and identify delivery systems, followed by animal testing and a series of clinical trials. This will be discussed in Chapter 3.

1.2.2 COMPLEMENTARY MEDICINE

CMs according to the Cochrane Collaboration cited by Vickers & Zollman (1999:693) are “a broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than intrinsic to the politically dominant health systems of a particular society or culture in a given historical period”. It is important to note that this definition – in keeping with most general discussions on CMs – do not refer to a specific cultural, religious or spiritual practice. Rather, CM can be understood as an umbrella term to denote practices of healthcare that stand in contrast to Allopathic Medicines.

CMs are commonly understood to focus on illness prevention and health promotion, rather than treating specific diseases. CMs are informed by cultural interpretations of disease, health and illness and the medications and practices are deeply rooted in specific cultures and are often intertwined with the historical-religious heritage of these people. Understandably, these vary considerably around the globe and are best understood from the specific context in which they are practiced. “Other commonly known names for CM are holistic, unconventional, natural, unscientific, non-orthodox, folk medicine, ethno medicine, mind-body medicine, unproven and non-allopathic” (Ernst & Fugh-Berman, 2002: 140). These alternate terms reflect not only the diversity of practices under the CM umbrella, but also the conflicting ways in which societies – and Allopathic Medical practitioners – view CMs.

1.2.3 SUMMARIZING KEY DIFFERENCES

The table below highlights the key differences between the two healthcare systems based on existing literature on the issue.

TABLE 1: Key differences between CMs and Allopathic Medicines as identified in the literature

CMs	**Allopathic Medicines**
It focuses on restoration of health (Adams & Jewel, 2007:2).	It focuses on the cure of diseases (Singh, 2010:20).
CMs proceeds with the notion that the mind, body and spirit are one (Mason et al., 2002:832).	Allopathic Medicines proceeds with a notion that the mind & body are separate entities (Mehta, 2011).
Treat a person as a whole, identifying the underlying causes and not simply removing a symptom (Adams & Jewel, 2007:2).	One of the guiding principles of Allopathic Medicines is treating or destroying a symptom (Siamak & Shirazi, 2012:1).
The patient plays an active role in the treatment process (Boon et al., 2006:25).	The patient does not play a role in the treatment process (Davis-Floyd, 2001:8).
Developed by folk knowledge (Charlton, 2002:643).	Based on clinical trials and scientific experimentation (Charlton, 2002:643).
“CMs use the original substance in its entity” (Ribeaux & Spence, 2001:189).	“The Allopathic approach separates the active ingredients and not use the rest” (Ribeaux & Spence, 2001:189).
"Illness is regarded as a deviation from health” (Verhoef&Hilsden, 1998:319).	“Health is regarded as a deviance from disease” (Verhoef&Hilsden, 1998:319).
“Reinforcing self-healing” (Bhika& Glynn, 2017:15).	“ Combating destructive or Infective” (Bhika& Glynn, 2017:15).

"Emphasises achieving good health. Focuses on lifestyle and prevention" (Bhika&Glynn, 2017:15).	"Emphasises achieving good health. Focuses on lifestyle and prevention"(Bhika & Glynn, 2017:15).

It is quite clear from table 1 that there are fundamental differences between CMs and Allopathic Medicines – both in the manner of treatment but also in the approach to the concept of health. Complementary health systems are involved in treating the person holistically by looking at both the mind, spirit and body while the Allopathic systems see the mind, body and spirit as separate entities (Moodley et al., 2008:153). Allopathic Medicines treat disease causing entities through pharmaceutical interventions, while CMs are concerned with assisting the innate healing powers of the body in illness management. In contrast, CMs rely heavily on testimonials and traditional use (Charlton, 2002:643).

Allopathic Medicines seeks to treat symptoms and CMs do not intend to directly target symptoms in the body. CMs and Allopathic Medicines also come from different cultural contexts in which disease and illness are variously interpreted. As evident from the table above stands in direct contrast to Allopathic systems. The CMs practitioner acts to assist the body in correcting the imbalances that contribute to the illness. This stands in direct contrast to Allopathic systems. According to (Ernst et al., 2003: 157), complementary interventions are "spiritual and social while allopathic interventions are directly measurable".

The history of Allopathic Medicine regulation also stands in direct contrast to CMs. Many CMs have evolved "organically" with the evolution of cultures and spirituality, with little in the way of formalized evaluation or regulation. In contrast, as the history of clinical trials attests, the last century has seen the rapid development of highly standardized regulatory processes for controlling the development and distribution of Allopathic Medicines. As discussed in section 4.3, this regulation has been motivated by a combination of historical, ethical and economic reasons.

CMs also tend to emphasize the importance of self-care in the patient as a means of promoting the body's self-healing abilities, rather than focusing on the disease itself. The CMs practitioner acts to assist the body in correcting the imbalances that contribute to the illness. This, as evident from the evidence above, stands in direct contrast to Allopathic systems. As a result, complementary interventions are "spiritual and social" while allopathic interventions are directly measurable (Ernst et al., 2004: 157).

Because of the highly individualistic interpretation of health, and the assisting role that the practitioner plays in health acquisition, it may be suggested that CMs focus more on individualized care. In contrast, the focus on disease-causing entities and interventions enables Allopathic Medicines to focus on standardized and generalizable care based on shared physiology. This raises an important question about how they can be brought together under one healthcare regulatory umbrella - in S.A. as much as on a global level.

CHAPTER 2- AIMS, RESEARCH QUESTIONS, OBJECTIVES, METHODS AND OUTCOMES

2.1 AIMS AND RESEARCH QUESTIONS

The main aim of this research report was to analyse some of the ethical issues that arised in the current governance of clinical trials of CMs in S.A and also offered some recommendations on how these issues could be addressed.

This research report questioned what areas of current oversight may be strengthened in order to maximise the benefits of conducting such clinical trials and to minimize the harms arising from them.

2.2 OBJECTIVES

The main objectives of this research was to:

a. Analyse current oversight of clinical trials in CMs in S.A.
b. To identify areas where the current legislation is not appropriate to CMs clinical trials.
c. To identify ethical and legal problems that may arise from these regulatory insufficiencies.
d. To offer recommendations on how these issues could be addressed.

2.3 METHODS

This research involved legal and normative research and analysis based on desktop and library based research. It was an ethico-legal research report drawing from the law and ethical literature relevant to the subject matter. No new data was collected or analysed. I employed the typical research methods and standards applicable to philosophical research including the interpretation and critical analysis of salient texts and the positing and defence of new arguments. My critical analyses of relevant texts included the definition and clarification of concepts, the identification and criticism of assumptions, the analysis and

evaluation of theoretical frameworks, the development and defence of arguments, the use of counter-examples, and the articulation of the most plausible interpretation of significant concepts found in the sources.

Sources of literature included and were not limited to articles at the University of the Witwatersrand University Library, Online Library Sources, Pubmed, Jstor, Wiley Science and Google Scholar.

The research did not involve study participants and ethics waiver (attached in Appendix A) was granted from the University of the Witwatersrand Human Research Ethics Committee (HREC).

2.4 OUTCOMES

Although research has been done on CMs, none has as far as I know have been done on ethical challenges faced in clinical trials of CMs in S.A and when I looked at other countries little research was done on this topic.

This research report will offer a range of recommendations for improvements in running clinical trials of CMs in S.A by having guidelines specifically for clinical trials on CMs. The absence of guidelines for clinical trials on CMs affects the approval of the clinical trials on CMs because what is applicable to Allopathic Medicine cannot be applied to a CM.

CHAPTER 3- REGULATING MODERN MEDICINES

This chapter outlines the history of clinical trials then the major difficulties encountered when applying randomised controlled trial (RCT) methodology to CMs clinical trials. It also gives other methods that could be used as alternatives to RCTs such as mixed methods studies and observational studies.

3.1 INTRODUCTION

'Standardization of medicines makes them to conform to a standard, consistent and also uniform. Standardization also ensures that the safety and efficacy are maximized (Folashade, Omoregie & Ochugu, 2012:102). According to Carissa & Califf (2016:213) "the regulation and standardization of medicines are important because it promotes and protects the public health by ensuring that:

- Medicines are of the required quality, safety and efficacy[3];
- Medicines are appropriately manufactured, stored, distributed and dispensed;
- Illegal manufacturing and trade are detected and adequately sanctioned;
- Health professionals and patients have the necessary information to enable them to use medicines rationally;
- Promotion and adverting are fair, balanced and aimed at rational drug use;
- Access to medicines is not hindered by unjustified regulatory work".

Issues on standardization are fundamental to modern understandings of just healthcare provision.

[3]Safety means tolerability and side effects while efficacy refers to whether or not it works.

3.2 HISTORY OF CLINICAL TRIALS

In Allopathic healthcare, clinical trials are widely agreed to be the best current form of standardization. Nonetheless, the recent attention paid to clinical trials does not denote new practices per se. Indeed, clinical research on human subjects dates back several hundred years, with the first documented controlled clinical trial was conducted in 1747 on 12 sailors with scurvy by Dr. James Lind. Through this trial he showed that citrus fruits such as lemon and oranges cured scurvy (Chalmers, 1981:326).

The first publicized blinded placebo-controlled randomized clinical trial was in 1946 which was performed by the MRC (Medical Research Council) in the UK(Jenkins & Hubbard, 1991: 228). This trial was reporting the effect of streptomycin on tuberculosis, and was the first one to randomly assign patients to experimental and control groups. This trial represented a significant advance in clinical trials methodology and contained features which remain fundamental to the design of clinical trials today. In the 20th and 21st century clinical trials have increasingly become the legally accepted mode of proving medicinal efficacy and safety, and are intricately connected to legislative and policy measures governing health.

3.3 THE MODERN CLINICAL TRIAL

According to South African Good Clinical Practice Guidelines (SAGCP)(2006:87), a clinical trial refers to “any investigation in human participants (including patients and other volunteers) intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining their safety and/or efficacy”[4].

Each clinical trial follows a protocol that defines the aim or rationale of the trial, defines the objectives, the design and methods used in the trial or the study (Hassim et al., 2007:390). Clinical trials in humans are conducted into four phases.

[4]For the purpose of this research report, that is the definition that will be used.

Phase 1 involves testing an active ingredient on a small number between 50-100 healthy participants or patients. The purpose of phase 1 is to evaluate the safety of the active ingredient, to determine the safe or acceptable dosage and also to identify potential side effects.

Phase 2 trials involve administering the medicine to a larger number of patients between 100 and 300 who currently experience the condition or disease to which the active ingredient is directed. This phase evaluates the safety and efficacy of the active ingredient (Hassim et al., 2007:390). Only once phase 2 evidence is available and has been assessed according to stringent standards (usually the MCC), permission will be granted to continue with phase 3.

Phase 3 involves a large number of people (500-1500 volunteers). Phase 3 evaluates the effectiveness of the active ingredient and the prevalence and types of side effects that it may cause. The medicine might be compared with currently used treatments on the market to determine its potential as an improved means of health provision. The final phase of studies is phase 4 which is the post-marketing surveillance (Gupta & Kohli, 2006:191). It is done after the medicine is registered. Its purpose is to collect additional information after the product is approved and marketed or to compare the medicine's efficacy with those of other medicines.

3.4 IMPORTANT ELEMENTS OF MODERN CLINICAL TRIALS

A randomized clinical trial (RCT) or randomized controlled trial is considered the gold standard of Allopathic Medicines research (Akobeng, 2008: 278). These assess the efficacy of the intervention in human beings by comparing the intervention to a control in groups that have been randomly assigned (Levin, 2007:22). Rajagopalan et al., (2013:32) suggests that RCTs are effective because they are "most like an experiment, it is the only effective method known to control selection bias, it is able to directly eliminate risk and it also allows comparison of multiple outcomes". In this way, RCTs cleave very strongly to current interpretations of the scientific method, and western science practices.

There are three important elements or features for RCTs (Grady, 2008:23), the first of which is randomization or random allocation. Randomization occurs when

two or more groups are compared and all participants have the same chance of either being assigned to the treatment or placebo (Iyioha, 2011:40). It is a chance rather than a choice and allocation is not determined by the investigators but rather by statistics.

The basic motivation for randomization is to prevent or eliminate selection bias, increases the internal validity (repeatability) and ensures that all variables have the same effect on all groups. Randomization also balances arms with respect to the known and unknown variables (Pihlstrom et al., 2000:16). Ones allocated to a group, participants will be asked to remain in it until the end of the trial.

The second critical feature of RCTs is blinding (Karanicolas, 2010:345), meaning that study participants, researchers and health care professionals do not know who is in the experimental group and who is in the control group. Blinding is a key marker of internal validity, as it reduces the possibility of bias – from the researcher, but also (through psycho symptomatic reactions) the participant. Zick et al., (2005:101) suggests that “blinding is an important method to also ensure the quality of a clinical trial. It improves participant compliance and retention in clinical trials. Lack of blinding usually leads to bias”.

Blinding can either be single, double-blind or triple-blinded (Akobeng, 2005:842). Single blind is an RCT in which one group of individuals involved in the trial does not know the identity of the intervention that is given to each participant. Usually, it is the participants or the investigators assessing the outcomes who do not know the identity of the interventions.

RCTs are usually conducted double blinded, where neither the trial participants nor the investigators or people collecting the outcome data are aware of any assigned intervention. For double blinding to be successful, the interventions must be indistinguishable – visually, in how they are administered, and how they taste/smell/feel - to both the participant and the investigator assessing the outcomes. Typically, the interventions are known simply as A or B and are

otherwise identical (Walker & Anderson, 1999:1616). Triple blind is when participants, the investigator giving the intervention and the one who evaluates it are all blinded. Triple blinding happens rarely.

The third element in an RCT is the presence of either an active control or a placebo that is administered to half the participants[5]. Active controls represent an existing treatment for the condition that is currently on the market. The existence of a control group enables the efficacy of the experimental drug to be effectively assessed. It must be noted that the use of a placebo (as a treatment without active ingredients) in clinical trials continues to arouse controversy – particularly in phase 2 and 3 trials where it results in sick patients not receiving treatment for the duration of the trial. According to Grace (2006: 58) using placebo in clinical trials is more about "deceiving patients and this is unethical as deceiving patients constitute a failure to respect their rights to make informed decisions thus a breach of ethical practice".

Clinical trials have developed synergistically with Allopathic Medicines, and may be said to closely reflect the perspectives of this system. Because of this, many of the key points – such as blinding, randomization and independent verification – strongly reflect the interpretation of disease as caused by biological entities.

3.5 REGULATING CMs WITH CLINICAL TRIALS: AN UNEASY FIT?

Most governments rely heavily on clinical trials for regulation and legislation as these trials offer evidence for or against efficacy and safety. This "objective" information makes it easy to legislate for or against the introduction of medicines into healthcare provision.

One could thus argue that to incorporate CMs into legislated healthcare provision it is feasible to assume that they should also be tested through clinical trials.

[5]Placebo is a pharmacologically inactive agent that investigators administer to participants in the control group.

Nonetheless, as evidenced in table 1, the manifold differences between these two systems of health provision must give pause for thought. How can systems of verification that focus on active ingredients and biological causes for illnesses be used to assess the efficacy of holistic health interventions?.

Indeed, many CMs practitioners or proponents of CMs have argued this point - that CMs should be exempted from the requirements of RCTs because the designs of RCTs are inappropriate to fit many forms of CMs therapies (Iyioha, 2011:2). They also strongly suggest that any results of testing CMs with RCTs would be misleading due to the impropriety of the mode of evaluation. Some argue that CMs have been practiced for so many years and there is anecdotal/traditional evidence so they do not need to be subjected to RCTs. These concerns are more fully discussed in below by focusing on the main elements of RCTs.

3.5.1 RANDOMISATION

As discussed in section 3.4, the randomization of trial participants to study or control groups is a key element in RCT design. This minimizes the possibility of selection, allocation, assessment and publication bias (Akobeng, 2008:841). As is suggested by the term, true randomization can only occur when all participants submit to being statistically divided into equal groups.

In CMs clinical trials such randomization might be hindered by the patient's strong preferences for a CM or practitioner's preference of one treatment over another making them unwilling to participate in studies where they are allocated to the placebo or control group. Randomisation might also affect the treatment effect (Verhoef et al., 2005:207). Unlike Allopathic Medicines, where the patient does not usually take part in the treatment process as indicated in Table 1, for CMs the active involvement of the patient in the healing process is key to the intervention's success. Thus, as Hamre et al., (2009:52) suggested, "the doctor-patient relationship in CMs therapies is very integral and it is disturbed by randomization", as could be the efficacy of the intervention.

3.5.2 BLINDING

As already mentioned in section 3.4, blinding prevents bias amongst researchers and participants. Blinding is an integral part of RCTs however how it can be achieved for many CMs is difficult to understand. Indeed, such blinding may be impractical or impossible as the practitioner and patient play integral roles in the healing process (Richardson, 2000:400).

Another key problem occurs through the need to have indistinguishable active and control treatments. According to Turner (2009:413), “the distinctive taste or smell of some herbal and alternative therapies poses a significant challenge to the appropriate blinding of study treatments”. Sharma (et al., 2010:277) stated that in Ayurvedic medicines it is always “difficult, impracticable or sometimes impossible to have active and control groups with identical colour, smell and taste. Indeed, it would be difficult to mimic the strong smell of ginger or garlic within a preparation (Bansal et al., 2010:18), or to administer a placebo massage or meditation.

3.5.3 ACTIVE CONTROL GROUP OR PLACEBO

The problems of blinding are similarly related to the difficulties of identifying appropriate placebo control group[6]. In acupuncture treatments[7] for example, the patient would often be able to tell if they are receiving the control and the experimental by the way the needles are inserted.

Moreover, as CM treatments often specialized for each patient rather than standardized to treat a hypothesized disease entity, finding a single control that could be effectively administered to a group of patients is difficult to imagine. Finally, it is not always clear whether interactions exist between herbal medicine and other medicinal products or substances like alcohol, caffeine, tobacco, nicotine or with diet. This also creates huge problems for the inclusion and exclusion criteria for clinical trials.

[6] Placebo control is a comparable therapy.

[7] In this research report, Acupuncture will be used as an example.

3.5.4 STANDARDISATION

It is also difficult to standardize the dosage of CMs in RCTs due to the lack of information about how (and why) treatments are effective. According to Verhoef et al., (2002: 276), the other reason it is so difficult to standardize CMs is that "there are wide variations in practice" that reflect the individual practitioner and their contextual training. As such, it would be very difficult to envisage how multi-site, multi-practitioner standardization could be achieved in CM clinical trials.

There are also a number of other issues to consider that relate to mind, spirit and body theories embraced by many CMs. This includes the importance of personal beliefs in CMs use, the involvement of the practitioner in the CM treatment experience, and the personalization of CM practitioning that may lead to a lack of standardization of CM practices (Mason et al., 2002:833).

Commercially produced CMs also vary according to manufacturers which make it difficult to standardize it. CMs are composed of many active components which are not yet identified and this makes standardization challenging. Other practical problems with CMs clinical trials as discussed by Osemene, Elujoba & Ilori (2011: 281) are "issues of dosage specifications, lack of proof of their efficacy, safety, proper problems, appropriateness of their degree or level of hygiene and cost of their production".

CMs such as Traditional Chinese Medicine (TCM) present further challenges, as they focus on symptom-complexes rather than individual diseases. These interventions describe the functioning of the whole body at a particular time and a particular stage of an illness. Because a symptom-complex is virtually unique to a particular patient, it is not possible to group patients for a study in a randomized trial as it is in Allopathic Medicines. Moreover, symptom-complexes are different for each patient, so the treatments of them are highly variably so. Walji & Boon (2006: 92) also stated that "RCTs cannot be used to examine the effectiveness of CMs due to conflicting theories of disease, lack of agreement about diagnostic criteria, contrasting view about the therapeutic process and different theories of causation".

3.5.5 PROPOSED ALTERNATIVE TO RANDOMISED CONTROLLED CLINICAL TRIALS

Envisioning effective RCTs for CMs is thus difficult, and there has been considerable discussion about the possible establishment of alternative methods of verification. Verhoef et al., (2005: 209), for example, proposed regulated individual observational studies as a possible alternative. Observational case studies are often suggested as an alternative to RCTs. Verhoef suggested that (2005: 209) “Observational studies are even less complex, less expensive to operate and they have strong external validity”. Benson & Arthur (2000:1878) also stated that “observational studies have greater timeliness, lower cost and a broader range of patients than the RCTs”.

There are three types of observational studies, namely case control studies, cross-sectional studies and retrospective/prospective cohort studies (Mariani& Pego-Fernades, 2014:1). While “RCTs have specific inclusion and exclusion criteria that are often restrictive, observational studies apply to a much broader population and are frequently even population-based” (Hannan, 2008:214). In observational studies, the population is not highly selective or there is no limit to the number of participants that can be included while in RCTs the population size is highly restrictive. According to Yang et al., (2010:S5) the restricted inclusion and exclusion in RCTs mean “that the type of patient enrolled into a particular trial bears little resemblance to the typical patient seen in the clinic”.

According to Yang et al., (2010:S4) cross-sectional studies “provide information on the prevalence of a particular condition at a single time point. These studies take a form of questionnaires and thus can be prone to responder bias in those individuals who give their time to respond to a questionnaire”. The main advantages of this study are that “As there is no follow up, less resources are required to run the study and they are quick” (Mann, 2003:57).

Case control studies compare groups retrospectively and are often used to generate hypotheses. “They aim to identify predictors of a particular outcome. The difficulty with case control studies is ensuring that cases and controls are a representative sample from the same source population. These studies can be

affected by recall bias" (Yang et al., 2010:S4). The main advantages of this study are that "it "Relatively quick to conduct and also inexpensive" (Song& Chung, 2010:17).

Cohort studies "takes a group of individuals who share a common characteristics (for example, a particular treatment, date of birth, or who have a particular disease. These studies are useful for identifying the incidence of a particular outcome over time" (Yang et al., 2010: S4). The main advantages of this study are that "it can examine various outcome variables and it is also much cheaper" (Mann, 2003:55).

According to Wardle & Roseen (2014: 144) "case reports continue to capture and describe important patient-centred clinical insights that may inform the individualised nature of contemporary patient care. Case reports can generate hypotheses for future clinical studies and also point to unknown risks or demonstrate regulatory or practice failures". Case reports can also identify new treatment options. The main advantages of case reports are that "answers can be obtained rapidly and they are inexpensive" (Manja & Lakshminrusimha, 2014:3).

Verhoef et al., (2005: 209) also proposed alternatives such as mixed methods research and appropriate outcome research. Mixed methods research "combines both the quantitative and qualitative research methods. Appropriate outcome measures the expected outcome of CMs interventions and practitioner" (Verhoef et al., 2005: 209). The values and beliefs of the patients are more easily captured using mixed methods research.

Qualitative research can assist in understanding the meaning of an intervention to patients as well as patient's beliefs about the treatment and expectations of the outcome (Verhoef et al., 2002:275). Both qualitative and quantitative researches are used to obtain a specific research question. This method also increases the internal validity of the research.

Pragmatic RCTs might also be applicable to CMs therapies as they take patient preferences into account. According to Patsopoulos (2011: 218) "The pragmatic trial is designed to test interventions in the full spectrum of everyday clinical

settings in order to maximize applicability and generalizability. The research question under investigation is whether an intervention actually works in real life*".* Pragmatic RCTs are designed to also ensure that external validity is taken into consideration. According to Williams et al., (2015: 1) "pragmatic clinical trials seek to answer important questions that are applicable to everyday clinical practice".

Nonetheless, such suggestions have not met with much favour in healthcare policy and legislative communities – particularly as RCTs have become such a fundamental means of assessing medical efficacy. There have been numerous articles published by different authors who outlined the limitations of alternative methods such as pragmatic trials, mixed methods and observational studies. In one of their articles, Ernst & Canter (2005: 203) stated that pragmatic trials are not the best tools that could be used as their "results are frequently next to meaningless". Another limitation of pragmatic trials is the fact that results that are used in S.A can never be applicable in the U.S.A for example. Even if it is the same country, clinical settings varies according to sites so the results can never be guaranteed.

The disadvantage of observational studies is that because of its lack of randomization there is a strong likehood of selection bias which makes this method one of the unfavourable methods to RCTs. According to Tariq & Woodman (2010: 6) using mixed methods is also problematic as "a quantitative and qualitative method belongs to a separate paradigm. Combining this two methods can be time consuming and requires experience and skills in both qualitative and quantitative methods".

In conclusion, this chapter highlighted main issues encountered when using the RCT method for CMs clinical trials. It also offered alternatives which could be used in place of RCTs. The next chapter will look more deeply into the deficiencies of the current system, SAGCP when applied to CMs clinical trials.

CHAPTER 4-STANDARDIZATION AND REGULATION OF COMPLEMENTARY MEDICINES IN SOUTH AFRICA

4.1 INTRODUCTION

The previous chapter provided a short history and evolution of clinical trials. It also highlighted issues which are currently faced when regulating CMs with clinical trials. In this chapter, I will give an overview of this and a critique of current issues.[8]

4.2 OTHER REGULATORY AGENCIES GUIDELINES AND CURRENT ATTEMPTS TO ADDRESS CLINICAL TRIALS OF CMs

Table 2 in the next page summarizes the guidelines for clinical trials in CMs/Traditional Medicine/Herbal Medicine of the different regulatory agencies. Clinical trials are necessary to test the efficacy and safety of those CMs which are on the market and those that are still going to be on the market. The WHO Guidelines for clinical trials of Traditional Medicines and the WHO Guidelines for Clinical Study of Traditional Medicines in the WHO Africa Region could be used as reference guidelines to draft the South African guidelines for clinical trials of CMs or could be incorporated into the current SAGCP.

The WHO guidelines “focus on the current major debates on safety and efficacy of traditional medicine and are intended to raise and answer some challenging questions. These guidelines present some national regulations for the evaluation of herbal medicine and also recommend new approaches for carrying out clinical

[8] For this research report, we make no distinction between OTC (Over the Counter) and prescription drugs. This research report works on the thought that all drugs should undergo testing before they are put on the market or released.

research. These guidelines will achieve their purposes of improving the quality and value of research in traditional medicine" (WHO, 2000: vi). "The Australian regulatory guidelines for Complementary Medicines provides information for manufacturers, sponsors, healthcare professionals and the general public on the regulation of Complementary Medicines in Australia" (ARGCM, 2016:11).

Table 2: Regulatory Guidelines for clinical trials of CMs/Traditional Medicines and/ or Herbal Medicines in other countries of the world.

Requirements for the clinical trials of CMs/Traditional Medicine or Herbal medicine	**WHO General Guidelines For Methodologies on Research and Evaluation of Traditional Medicine**	**Australian Guidelines for CMs(ARGCM)**	**Botanical Drug Development Guidance for Industry(FDA)**	**MCC(SAGCP)**
Traditional Use	It is considered in the evaluation of safety and efficacy(WHO,2000:24)	Use of Traditional Medicine must be well established and widely acknowledged (ARGCM, 2016:115).	Traditional use is not considered in the evaluation of safety and efficacy(FDA,2016:28)	Traditional use is not considered in the evaluation of safety and efficacy.
Safety	"Documentation of a long period of use should be taken into consideration when evaluating safety" (WHO, 2000:24). "Toxicity studies should be performed when there is doubt about the safety" (WHO, 2000:6).	"It may be established by detailed reference to the published literature and/or the submission of original data" (ARGCM, 2016:115).	Requirements are the same as for Allopathic Medicines(FDA,2016:28)	Requirements are the same as for Allopathic Medicines.
Efficacy	WHO (2000:25) "Where traditional use has not been established, appropriate clinical evidence should be required" to evaluate efficacy.	"Safety may be established by detailed reference to the published literature" (ARGCM, 2016:114)	Requirements are the same as for Allopathic Medicines(FDA,2016:28)	Requirements are the same as for Allopathic Medicines.

4.3CURRENT PROCESS OF CMs REGISTRATION IN SOUTH AFRICA

As mentioned already, “the WHO estimates that 80% of the world’s population use CMs as their primary source of healthcare and similar figures have been reported in the South African population”(Siegfried & Hughes, 2012: 2). Nonetheless, until 1982 there was no definition of CMs in S.A and the types, extent and administration of CMs within communities was poorly documented.

The current definition of CM in S.A[9] according to the Medicines Act “ means any substance or mixture that a) originates from plants, fungi, algae, seaweeds, lichens, minerals or animals or other substance as determined by Council; b) is used or purporting to be suitable for use or manufactured or sold for use, i) in maintaining, complementing, or assisting the innate healing power or physical or mental state, or ii)to diagnose, treat, mitigate, modify, alleviate or prevent disease or illness or the symptoms or signs thereof or abnormal physical or mental state, of a human being or animal ; c) is used i)as a health supplement, or ii) accordance with those disciplines as determined by Council or d)is declared by the Minister, on recommendation by the Council, by notice in the Gazette to be a Complementary Medicine”. Interestingly, however, this remains a proposed definition and still needs to be formally ratified.

WHO defines traditional medicine as quoted by as (Hassim et al.,2007:202) “diverse health practices, approaches, knowledge and beliefs incorporating plant, animal and/or mineral based medicines, spiritual therapies, manual techniques and exercises applied singularly or in combination to maintain well-being, as well as to treat, diagnose or prevent illness”.

[9]Proposed Amendments to General Regulations made in terms of the Medicines and Related Control Act No 101 of 1965(25 July 2016).Proposed addition of Health Supplements is under review. To effectively regulate medicines in S.A, CMs have been separated from the African Traditional Medicines (ATM). The term CM is used interchangeably with Traditional Medicine (TM) in some countries but not in S.A. For the purpose of this research this will be the definition of CM that will be used.

Similarly, until November 2013 there was no legislative framework for the control of CMs (manufacturing, distribution and use) within SA. This was due to the fact that there was no regulatory framework in place such as guidelines and regulations specifically for CMs. On the 22nd February 2002, the National Department of Health (NDOH) through Medicines Control Council (MCC) published a Call Up Notice[10] which requested importers, consumers, wholesalers, retailers and manufacturers of CMs to submit limited information for audit purposes only not for registration purposes for products already on or about to enter the market at that time for a period of 6 months.

The purpose of the Call Up Notice was to see which products are on the market and also which are entering the market but instead this Call Up Notice caused so much confusion amongst the importers of CMs and the industry as many thought this was the registration process. This process was very flawed as it did not ask many questions regarding the safety, efficacy and quality of the product.

Currently, CMs applications are submitted on a ZA-CTD Form[11]. The application form is obtainable from the MCC website where all the information pertaining to the registration of medicines including guidelines and fees are also available. This call for registration thus places the MCC under obligation to evaluate and pronounce on the quality, safety and efficacy of CMs. In so doing, it has become necessary to subject CMs to a form of independent, reproducible and verifiable system of evaluation for all CMs.

Currently, CMs in S.A are divided into discipline specific and health supplements. Disciplines specific CMs are “Aromatherapy, Ayurveda, Homeopathy, TCM, Unani Tibb Medicine and Western Herbal Medicine” (Fourie, Oosthuizen& Du Toit: 2017: 484). Types of health supplements are probiotics, prebiotics, vitamins, minerals, amino acids, animal extracts, carotenoids, bioflavonoids, amino saccharides, saccharides and enzymes.

[10]-Call Up Notice No R204, Regulation Gazette No 7282.

[11] CTD stands for common technical document.

Clinical trials have been proposed as the easiest way in which to address safety and efficacy of medicines, however – as outlined above – this is deeply problematic. It is further problematic due to the fact that there are no guidelines at the moment specifically addressing clinical trials in CMs and the SAGCP guidelines used are not compatible with CMs clinical trials. There is thus a tension between the need for regulation and perpetuating a flawed system of evaluation.

4.4 SUBJECTING CMs TO CLINICAL TRIALS IN S.A: CURRENT REGULATIONS

The current legislative regulatory framework for the control of clinical trials in S.A is the SAGCP guidelines which were published in 2000 and updated in 2006. These guidelines are guaranteed by the South African National Health Act of 2003[12] and are similar to the International Conference on Harmonization Good Clinical Practice (ICH-GCP). These guidelines – unsurprisingly – are designed for the regulation of RCTs on Allopathic Medicines. They thus emphasize the norms of clinical trials such as double blinding, randomization and standardization.

The SAGCP guidelines are intended to ensure that the clinical data are credible. It also protects the rights, safety and well-being of trial participants. A clinical trial in S.A may not commence until approval by both the MCC and the local ethics committee is obtained. The second guideline which is referred to with regard to any research in human participant in S.A is the Research Ethics Guidelines which was updated in 2015 by the National Department of Health (NDOH[13]).

At present, there are no guidelines or any legislation framework in place specifically for clinical trials on CMs in S.A. Nonetheless, the SAGCP guidelines (2006: 12) stated that in the absence of guidelines for CMs the SAGCP

[12] Section 90 of the National Health Act, Act No 61 of 2003.

[13] Ethics in Health Research: Principles, Structures and Process. Department of Health. Pretoria. 2015.2nd Edition.

guidelines[14] can be used to guide any research on human participants. As the SAGCP guidelines are designed for use in clinical trials for Allopathic Medicines, their use thus further complicates an existing problem. Moreover, the SAGCP guidelines do not engage with alternative ways of assessing.

Indeed, the guidelines do not addressed issues such as criteria for standardization of CMs or take into account the individuality of each CM therapies. As already mentioned in chapter 3, randomization is difficult or challenging for some CMs clinical trials and in the SAGCP guidelines there is no mention of how best to solve this problem. WHO guidelines (2000: 14) clearly stated that "where randomization is impossible, the best way to solve that problem is by proper selection of the control treatments". WHO guidelines for Clinical Study of Traditional Medicines in the WHO African Region stated that "pseudo-randomization method may be adopted by using block randomization where a balance will be achieved for every sixth or patient". The SAGCP guidelines (2006: 53) only mentioned that "in the case of randomisation of participants, the procedure must be documented".

Furthermore, there is no mention of what should be done in cases where it is difficult to blind in the SAGCP guidelines. As mentioned in the previous chapter, blinding is difficult in clinical trials of CMs. WHO guidelines (2000: 15) stated that "it is important to note in the evaluation of study that blinding was difficult". There is also no mention of how CMs safety can be assessed and supported in the SAGCP guidelines.

The WHO guidelines (2000: 24), FDA: Guidance for Industry: Botanical Drug Products(2016:15) and Australian Regulatory guidelines for CMs (2016: 114) clearly mentioned that the safety of CMs, botanical drugs or traditional medicines can be supported by the traditional use or long period of use and also published literature/peer reviewed scientific papers and bibliographical evidence from books and pharmacopoeias, must be presented along with the application to prove traditional use or long period of use. The Australian Regulatory guidelines for CMs

[14] There are other important documents dealing with various aspects of CMs, such as Intellectual Property Systems (IPs) but they are beyond the scope of this research report to discuss in detail.

(2016: 75) further states that when traditional used to demonstrate safety you also need to look at certain number of people who used those CMs. It further states (2016: 163) that “you must clearly indicate whether the substance under review is the same as that used traditionally, that is: the same plant part, preparation, dosage and dosage form”.

The SAGCP guidelines also do not explain about what happens if there is no documentation of traditional use. The WHO guidelines (2000: 6) clearly states that “if there is no documentation of traditional use then toxicology should be performed”. There is no way in the SAGCP guidelines whether it mentions what kind of information is needed to support claims based on evidence of traditional use[15] and also the scientific use of a CMs. The WHO guidelines make guidance with the type of information which must be submitted for claims on both the traditional use and also scientific evidence. FDA guidelines for Industry: Botanical Drug Products (2016:15) clearly states that “if there are no prior human experience or known safety issues, additional early-phase clinical data should be provided before initiating larger-scale, late phase clinical studies.

The SAGCP guidelines urgently need to be revised, as to make clinical trial guidelines for CMs acceptable as part of good clinical governance. This requires considerable further research and investigation. First and foremost, there is the need that “clinical research aimed at evaluating traditional medicine should incorporate research designs, such as randomized controlled trials or observational studies” (WHO, 2000: 11). Further research is also necessary on the efficacy on other means of evaluation, such as mixed methods research, observational studies, case studies and case reports.

The development of SAGCP oversight for CMs would also benefit from the experiences of other regulatory agencies such as WHO, FDA and TGA. These have all recently developed guidelines for clinical trials in herbal medicines. While,

[15] According to WHO (2000:41)“traditional use refers to documentary evidence that a substance has been used over three or more generations of recorded use for a specific health related or medicinal purpose”.

of course, the unaltered re-use of these guidelines is inappropriate, an in depth analysis of them could add value to the SAGCP.

In conclusion, having looked at SAGCP guidelines, what it overlooks in terms of CM clinical trials, the current problems that are faced can be summarized as follows:

i. The government is under obligation to provide guidelines for clinical trials of CMs and to regulate CMs clinical trials.
ii. SAGCP guidelines developed for Allopathic Medicines are problematic for CMs clinical trials.
iii. There is no inclusion of other alternative methods such as observational studies.

The next chapter will examine some of the ethical issues that arise when incompatible regulatory policies, such as the SAGCP, are used to regulate CM clinical trials. It will focus on a range of different issues relating to the participant, the practitioner, but also the scientific and medical professions more broadly.

CHAPTER 5- ETHICAL PROBLEMS WITH CONDUCTING CLINICAL TRIALS WITH COMPLEMENTARY MEDICINES: ACCORDING TO THE SOUTH AFRICAN REGULATIONS

In section 4.4 of the last chapter, I looked at problems encountered when applying SAGCP guidelines to CMs clinical trials. In this chapter, I will be looking and discussing the ethical issues encountered in the absence of guidelines for clinical trials of CMs or the ethical issues that arises when SAGCP guidelines are used for clinical trials of CMs. The recognition of these ethical issues makes the formation of new regulation for CM clinical trials not only desirability, but an ethical necessity. Unpacking these issues clearly illustrates the impropriety of continuing with the current status quo, and the maleficence of the government perpetuating of a flawed system of regulation. Such issues to be considered include the failure of the government to protect the public, the high costs of conducting RCTs with few viable returns, and the burden of unnecessary participant involvement.

This chapter focused on participant-related issues due to the need to limit the scope of the research report, but other key issues will deserve attention in the future, such as issues relating to liability, ownership and IP, and public/private responsibility. The chapter focused on participant-related issues as these have the potential to cause the most direct harms if not protected in CM clinical trials. These concerns map well on to broader discussions on RCTs and therefore give considerable scope for evaluating harms/benefits of CM RCTs against a highly examined backdrop of patient protection in RCTs more generally.

The chapter also focused on issues of governance and policy for example in page 32 where it states that flawed or incompatible guidelines affect issues of informed consent. In page 31 as well it shows that the lack of guidelines for CMs clinical trials also leads to poor regulation and this place RECs in a difficult position. These issues are all related to policy and governance issues.

5.1. CONSIDERING THE SCIENTIFIC VALIDITY FOR CMs CLINICAL TRIALS

Validity in RCTs demands sound scientific practices to ensure the accuracy of scientific findings so that the study yields reliable information. “Scientific validity relies on internationally accepted principles of research practice and should be considered an ethical requirement of any research or a prior condition for any ethical research”(Freedman 1987: 7). This ethical imperative stems from a number of different observations relating to why it was appropriate to conduct the study.

First, “the ethical justification of scientific validity for any clinical trial/s relies on the principle of the avoidance of exploitation of participants” (Naidoo; 2014: 37). At its most primary level, this refers to the inacceptability of participants assuming the risks of any RCT if the trial itself cannot produce useful results. It therefore follows that a study can only be ethical if the methods employed can be feasibly assumed to yield scientifically valid results.

Scientific validity consists of two aspects the external and internal validity. According to Tilburt & Kaptchuk (2008: 596) internal validity means that “the research must reliably test hypothesized relationships between an intervention and an outcome under controlled conditions. Internal validity tries to answer the research question”.

Chapter 3 stated that blinding enhances and protects internal validity and also assists in avoiding bias. Nonetheless, as discussed, blinding is difficult or impossible in some CMs clinical trials because the practitioner is an important part of the intervention. Internal validity is dependent on appropriate randomization and blinding. CMs clinical trials lack internal validity as randomization and blinding are at times difficult to achieve. The unique characteristics of CMs also make it difficult to obtain internal validity. RCTs also have higher internal validity and it is difficult or impossible to conduct a RCTs of CMs.

External validity[16] is defined by (Millard et al., 2014: 2) as “the extent to which results can be generalized to other circumstances”. In order for the research to be of any use, it must be possible to generalize the results. External validity is often difficult for some CMs clinical trials because it might be difficult to generalize the results from a formal and structured clinical trial as it is done in Allopathic Medicines. The current SAGCP guidelines undermine scientific validity because the guidelines are specifically for Allopathic Medicines as already discussed in the previous chapter and not for CMs and it is inevitable that when they are used for CMs clinical trials they will be found not to be suitable. The SAGCP requirement for CM clinical trials must cause concern as to what types of information are being generated by these trials as some of those trials are not providing useful information.

Some CMs clinical trials also lack external validity due to lack of strict standardization as discussed in chapter 3. RCT usually provides valid and reliable results to be used in clinical research but in CMs clinical trials they are at times impossible or difficult to conduct as already discussed in the previous chapter. CMs clinical trials often lack randomization or it is difficult to randomize as discussed in Chapter 3. Randomization increases internal validity, thus lack of randomization results in poor internal validity. Without internal validity, the clinical trial is meaningless and unethical.

Lack of scientific validity for some CMs clinical trials leads to compromised research and undermines the justification for doing the research. In addition to providing invalid information of the CMs in question, and exposing study participants to unnecessary harms, the lack of validity caused by inappropriate study design can have far reaching effects. As RCTs involve considerable resources, conducting trials with questionable validity waste time, manpower and financial resources that could have been more effectively spent elsewhere. Indeed, in a resource-constrained country such as S. A., any profligacy with national resources must be considered highly inappropriate.

[16] Other words for external validity are generalizabilty, applicability and transferability.

Moreover, poor understanding of CMs or unrepresentative information on CMs could lead to poor policy decisions by the government, compounding an already complex system of national health provision.

5.2 CONSIDERING THE PROTECTION OF PARTICIPANTS IN CMs CLINICAL TRIALS IN S.A

The protection of trial participants is a fundamental element of any study design. It is commonly agreed that “even though risks are inevitable in clinical trials, it is important that those risks are assessed and minimized and that any anticipated harms be monitored, reported and managed” (Califf et al. 2003: 257). While the researchers are obligated to ensure that the risks of participation are as low as possible, it is commonly assumed that participants are willing to take on these risks due to the range of benefits also associated with participation.

According to Bake (2006: 13) benefits of participating in a clinical trial includes the following: “playing an active role in your own health, gaining access to the new research treatment way before they are available to the public, obtaining expert care as highly qualified and leading facilities are there during the trial and lastly being able to help others by contributing to the medical research.”

Clinical trials oversight is a very important element in ensuring the protection of participants. According to Dhai & McQuoid-Mason (2011: 170) the safety of participants in clinical trials in S.A are protected by the Research Ethics Committees (RECs) of research institutes, Data and Safety Monitoring Boards (DSMBs) and MCC These committees which are charged with overseeing clinical trials uphold the three basic principles of Belmont Report which are Respect for Persons, Beneficence and Justice.

According to the SAGCP(2006: 58), the RECs also “provides public assurance of the protection by reviewing, approving and providing comment on clinical trial protocols, the suitability of the investigator(s) and procedures used to obtain informed consent. The RECs are guided by the relevant South African ethical guidelines”. The main role of the RECs is to safeguard the dignity, rights, safety,

and well-being of all trial participants in clinical trials (Califf et al., 2003: 257). They are also expected to judge protocols based on scientific merit and the expectation of valid results. RECs are expected to take full responsibility of the clinical trial they approve as well as protect the participants from the harm that may arise from poor research.

As already discussed in section 4.4 of chapter 4, there are currently no guidelines specifically for CMs clinical trials in S.A and poor regulation of CMs clinical trials thus places RECs in a difficult position as they must pass judgment on unclear protocols. In the absence of guidelines for CMs clinical trials, the risks to the patients cannot be properly assessed as there will be no standards to adhere to. This has a huge impact on the mandate of the RECs as they will not be able to protect the welfare of the participants in the absence of guidelines. This places unnecessary strain on RECs, and can lead to serious complications including the undermining of the authority of the REC as well as personal challenges for individual members.

The RECs have a legal obligation to the government for patient safety according to the National Health Act. In terms of law, the National Health Act has provisions for the protection of the participants and researchers who ignore or fail to adhere to those provisions may be guilty of a criminal offense. This Act is enforceable and has powers to prosecute. The protection of participants in health-related research is also supported by international documents such as World Medical Association's 1964 Declaration of Helsinki, Belmont Report and the Council of International Organizations of Medical Sciences International Ethical Guidelines. Thus, the perpetuation of potentially flawed CM RCT study designs can cause considerable problems for those appointed to positions of responsibility and authority.

5.3 INFORMED CONSENT AND AUTONOMY

Linked to issues of patient protection is the importance of informed consent in clinical trials, which reflects the obligation to respect persons and their autonomous decisions (Beauchamp & Childress, 2009: 119). It is expected that

when informed consent is adequately administered that a person is accurately informed of the purpose, methods, risks, benefits of the research and gives an un-coerced decision to participate (Beauchamp & Childress, 2009: 120).

Respect for autonomy and informed consent are inseparable (Hall et al., 2012: 533). “The elements of adequate informed consent include full disclosure, comprehension of information, voluntariness and competence to consent” (Beauchamp & Childress, 2009: 120). This reflects a three stage process, where the participant is given full and accurate information about the purpose of the RCT, the possible risks, and the extent of their expected involvement. They then have the opportunity to reflect and question the information given, before making an autonomous decision about their possible involvement.

Flawed guidelines for CMs clinical trials in S.A tend to overlook the difficulties of informed consent. For an example, CMs therapies have a spiritual component so it may be necessary to describe that in the guidelines. The SAGCP guidelines (2006: 11) only state that “obtaining informed consent implies the provision of information to potential participants regarding the nature of the research procedure, scientific purpose and alternatives to study participation” and it does not state anything about a spiritual component of CMs. Some researchers in CMs clinical trials do not disclose or inform participants about the spiritual component of CMs and this is problematic as it limits consent and it is not full disclosure.

There are also instances whereby the researchers in CMs clinical trials undertake to give a CM to participant/s without knowing what the active constituent is or even other substances/ constituents, what the correct dosage is and also what risks are involved. In these instances, it is really impossible for participants to consent or this limits the process of informed consent as one cannot give consent to the unknown. The process of informed consent involves disclosing the risks and benefits of the trial.

Current guidelines thus place both practitioner and patient in difficult positions. The patient’s ability to make informed autonomous decisions is impacted by the lack of information about CM actions and efficacy, which potentially exposes them to unforeseen risks. Conversely, the practitioners, by not being able to offer such

information, are not able to fulfil their duties to beneficence and non-maleficence as expected by their profession and peers. Both, thus, are compromised in their abilities to act as autonomous agents.

5.4 RESEARCHER INTEGRITY

Performing research or a clinical trial requires integrity. According to Piacentini (2013: 21) “to have integrity in a research is to aim for wholeness, positivity and to produce workable frameworks that enhance performance in the research field”. Without integrity, there is no accountability and the ethical, careful and honest measures we put into place to ensure we protect our participant’s confidentiality will fall apart. In a clinical trial, a researcher must adhere to moral principles. According to Dhai & McQuoid-Mason (2011: 32) “researchers should incorporate these core ethical values and standards as the foundation for their character and practice as responsible researchers”.

Lack of guidelines for CMs clinical trials as it is the situation right now in S.A may put researchers into difficult situations or ethically compromising moments as they cannot commit to fully safeguarding participants in instances of harm or may not know what to do. Secondly, in the absence of guidelines for CMs clinical trials, there will be no standards to adhere to and this can facilitate researchers towards non-compliance and this may have a huge significance for patient safety. The flawed system may also put an unaware researcher in a compromised position of not performing the clinical trial to the highest standard of professionalism and in an ethically robust manner. Flawed systems can also test the unaware or not adequately trained researcher’s ability to maintain ethical standards.

Heimer (2013: 373) in her article mentioned that “if people do not have any place to sit while they do their work, they are likely to fill out the forms correctly or check them. If there is not a clock, they can’t document the time if they don’t themselves own watches. If there is not locking cabinet, they can’t store their work securely”. This can be applied to the current situation of lack of guidelines for CMs clinical trials. If there are no guidelines, researchers cannot be expected to try and be ethical. Researchers may also not follow any protocol when running the clinical trials of CMs as there are no systems in place. In the absence of guidelines the

researchers cannot guarantee or secure safety for participants as mentioned previously. In conclusion In conclusion, the government should not have any expectations that those researchers in CMs clinical trials to be ethical unless they have systems in place such as the much needed guidelines for CMs clinical trials.

5.5 GOVERNMENTAL RESPONSIBILITY

The government has obligations to improve health provision. These responsibilities are in line with the three key ethical principles identified in bioethics: beneficence, non-maleficence and justice. The government has key responsibilities to the public to uphold all three – something that is undermined by the current status of CM RCTs in S.A.

The principle of beneficence in bioethics involves the obligation to promote good, act in the best interest of others and the society to prevent, remove, minimize harm and risk and also promoting and enhancing the good of a person (Dhai & McQuoid-Mason, 2011: 14). This principle gives rise to norms requiring that the risks of research practice to be reasonable in the light of the expected benefits, that the research design is sound, and that the investigators or researchers be competent both to conduct the research and to safeguard the welfare of the research subjects.

In order to maximize the benefit to the participants of CMs clinical trials, the S.A government should ensure that guidelines on CMs clinical trials are drawn and put into place. By not having guidelines for CMs clinical trials, society is not benefitting at all. This also puts the promise of healthcare to the population in jeopardy. It also wastes resources and time. Clinical trials as discussed previously are beneficial as new drugs could be discovered which will reduce the burden of high disease rate.

Principle of beneficence is closely related to the principle of non-maleficence. According to Beauchamp&Childress (2009: 149) “The principle of non-maleficence imposes an obligation not to inflict harm on others”. The government has a strong obligation towards non-maleficence as exemplified in the Batho Pele principles. By allowing RCTs to continue when the REC oversight and researcher integrity can be potentially compromised by the inappropriate guidelines, the government

violates the principle of non-maleficence. Indeed, they voluntarily perpetuate situations in which participants are potentially placed at risk.

The principle of justice is defined by Beauchamp & Childress (2009: 241) as the "fair, equitable, and appropriate treatment in light of what is due or owed to persons". This principle recognizes that people should be treated fairly and in accordance with what is morally right. "The principle of justice is an important factor in resource allocation decisions" (Dhai & McQuoid-Mason, 2011: 145). The promotion of flawed guidelines for CMs clinical trials could result in a waste of resources, wastes time, and this as stated in the last paragraph puts the promise of healthcare for the population in jeopardy. In resource-limited healthcare system like the one in S.A, guidelines are needed to improve the efficiency of health care , cost effectiveness and to free up resources needed for other healthcare services**.**

The government is perpetuating non-effective medicines to be part of the health provision in the absence of guidelines. It can also be said that due to lack of guidelines for CMs clinical trials, the society is also being robbed of medicines which might be effective in the treatment of diseases.

CHAPTER 6: SUMMARY AND CONCLUDING REMARKS

Despite the issues identified in chapter 5, S.A. still needs some form of oversight for the clinical trials of CMs – particularly as S.A moves towards a more universal and government-mediated healthcare system such as the NHI which will ensure that all South Africans have access to quality health care services. Thus, we have to ask, what systems could assist in better regulating CMs? This chapter concludes the report and makes recommendations for clinical trials of CMs in S.A.

6.1 RECOMMENDATIONS FOR CMs CLINICAL TRIALS IN S.A

This section will provide recommendations on how to conduct CMs clinical trials in S.A. As stated in the previous chapters, there are currently no specific guidelines or framework in place for clinical trials of CMs in S.A. The absence of guidelines for clinical trials of CMs in S.A affects the approval process of clinical trials of CMs.

6.1.1 POLICY MAKERS

There is an urgent need of comprehensive review of current policy and the development of specific policies for CM clinical trials. The MCC should establish a clinical trial Sub-Committee for CMs/Plant Based Medicines which will be responsible for developing guidelines that are appropriate, relevant and specifically for clinical trials of CMs or Plant-Based Medicines. The Sub-Committee should be given a specific time limit to complete the development of those guidelines as there is an urgent need of these guidelines.

The Sub-Committee should compromise of members with interest in clinical trials of CMs. The different stakeholders should also be involved in the development of guidelines for CMs such as researchers, Allopathic Medical Doctors, CMs practitioners, the pharmaceutical industry and healthcare policy makers. It is possible that the CSIR (Council for Scientific and Industrial Research), MRC and the NDOH could work together to collate all existing knowledge of CMs into an easily accessible database.

6.1.2 FOR FUTURE CMs RESEARCH

The MCC should initiate properly designed and conducts RCTs of all CMs. Even though some of the CMs cannot meet the criteria established for Allopathic Medicines as already discussed in Chapter 3, the MCC must work with clinical research organizations to address these issues in order to evaluate CMs products. The clinical trials sub-committee for CMs/Plant Based Medicines should be guided by the international regulatory agencies such as WHO and Australian guidelines for the development of the guidelines.

The guidelines should also state that traditional use of CMs should not be a substitute for safety but must be taken into consideration when safety is evaluated. When traditional use is used as safety evidence, the details of use (such as duration, route, dose, etc) should be consistent with the proposed use. Where data of traditional use is insufficient, the safety evaluation will need to be supported with other studies such as animal studies and more basic science studies.

The guidelines should also accommodate CMs products that are already on the market. For those products because of their long-term use, phase 2 and phase 3 studies may be conducted while those products are on the market. The dosage form was not mentioned in SAGCP guidelines. The dose of any CMs will only be determined by the dose used by the CMs practitioner.

It is also necessary to develop a new method for the evaluation of CMs to use in place of the current RCT approach. There is evidence of alternatives (such as case control studies, cross-sectional studies, cohort studies and case reports studies discussed in section 3.5.5, pages 17-18). These may provide some solutions to the ethical and practical problems listed above, but require considerable further investigation.

While authors such as Verhoef (2005) recognize the benefits of these alternative methods, more empirical evidence needs to be gathered before they can be

reliably recommended as alternatives to RCTs. Indeed, it is possible that a new "middle ground" between RCTs and these alternative methods also need to be explored. We need more understanding of where the current approach is failing and new evidence on alternatives.

RCTs for CMs show clear evidence of potential participant harm. Therefore, new strategies that address: a) the inability to adequately consent participants, b) control for unexpected outcomes in a more regulated manner and c) allow for scientifically valid and valuable comparisons between treatment regimes.

As described above, in order to advance the current framework we first need to know where the current framework failed in order to give it a new direction. The current guidelines do not suits CMs clinical trials as described in Chapter 3. Some areas of the guidelines need to be changed to accommodate the individual needs of CMs. I would suggest that other regulatory agencies guidelines such as WHO and FDA be critically examined for ways in which they could contribute towards developing the SAGCP. Alternatively, new guidelines for CMs clinical trials need to be drafted.

6.2 CONCLUDING REMARKS

Investigations into the safety of CMs are important and necessary to safeguard the interests of the public. The various methods can be used to determine the safety and efficacy of CMs but it is very important to know of these options in order to always carry out the best possible research. Safety must never be assumed but it must be demonstrated using adequate research methods. The challenges currently faced in CMs clinical trials in S.A can only be overcome by having a set of guidelines specifically for CMs clinical trials. The government need to ensure that there are guidelines for CMs clinical trials in order to uphold the principles of non maleficence, beneficence and justice.

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Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH10005, 10th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: P V Tobias Health Sciences Building, 2nd floor Tel +27 (0)11-717-2700
Private Bag 3, Wits 2050, www.wits.ac.za. Fax +27 (0)11-717-1265

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Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical).

Investigator: **Mmabatho Ledile Malesela (Student no, 507886).**

Project title: **An analysis of ethical issues arising in the current governance of clinical trials for complementary medicine in South Africa: looking towards the future (Changed title and name).**

Reason: This study is an analysis of information in the public domain. There are no human participants.

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