Determining the Benefits Realization Management Practices and Processes in Clinical Trials

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iii. Abstract

Benefits are measurable improvements that result from project outcomes. There is an emphasis in clinical trials literature that clinical trial benefits must always outweigh the risks yet there is limited clarity on processes to manage and ensure delivery of those benefits. With uncertainty around the delivery of clinical trial benefits, it is worth adopting a balanced management approach. This study looked to establish whether there were any comprehensive benefits management processes in HIV clinical trials and compared these practices to those described in the literature.

Methods: To assess the current benefits management practices used to manage HIV clinical trials, a cross-sectional study used a critical review of clinical trials guidelines and publications as well as an online survey that was distributed to stakeholders in clinical trials management.

Results: The critical review of the guidelines and literature revealed a high emphasis on risk-benefit assessment, but very limited mention of the processes used for the assessment and management of those risks and benefits. The diverse group of clinical trials managers that responded to the online survey were involved at the strategic level of their respective clinical trials and 74% of them had never heard of Benefits Realization Management (BRM) and BRM processes. The respondents however, acknowledged that their lack of awareness did not necessarily mean lack of existence of BRM or BRM processes in HIV clinical trials. There were aspects of benefits management practices in clinical trials that were found to be similar to those in literature and other industries such as benefits planning, benefits identification, benefits review, setting time scale to benefits realization and allocating benefits champions. Even though there was confidence from the respondents in how clinical trial benefits were managed and in clinical trials delivering their promise, the respondents still believed there was room for improvement in the current BRM processes.

Conclusion: BRM processes are not readily visible or documented in HIV clinical trials. There is a management bias towards safety and ethics in clinical trials which seems to have resulted in

limited focus on benefits management. Compared to other industries, there appears to be more room and opportunity to implement published BRM processes. The findings from this study will serve as a starting point for future studies on how BRM can be incorporated into current management practices in order to achieve the most out of clinical trials.

Key Words: *Benefits Realization Management, Processes, Clinical Trials, Strategy*

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To my sons Letlotlo and Mohau, I love you and I am doing all this for you.

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List of Abbreviations

BRM – Benefits Realization Management

IS – Information Systems

IT – Information Technology

PMBoK – Project Management Body of Knowledge

PMO – Project Management Office

HIV – Human Immunodeficiency Virus

AIDS – Acquired Immune Deficiency Syndrome

HVTN - HIV Vaccine Trials Network

IRB – Institution Review Boards

WHO – World Health Organization

1 Introduction

1.1 Summary

Clinical trials are initiated to test a drug or treatment regimen that is in the research and development stage. The treatment or regimen is intended to improve the quality of people's lives or improve the current treatments towards some ailment. The managers of clinical trials should then keep a close eye on the strategic reasons for conducting the clinical trial throughout all phases of clinical trials.

There is plenty of uncertainty that comes with any research. Clinical research specifically impacts people's lives. It is thus worthwhile strengthening management styles to focus the clinical research efforts and improve the chances of positive outcomes. There has to be a balanced approach in managing strategic goals and the day to day issues such as enrolling a significant number of people, issuing the drug/intervention and collecting data to guarantee delivery of value or benefit.

This research dissertation reports on a cross-sectional assessment of current practices and processes used for managing HIV clinical trials. The study looked into project management processes used in managing HIV clinical trials with specific focus on benefits realization management (BRM). This study attempted to establish any awareness or application BRM frameworks within the HIV clinical trials as proposed in literature. This was done by reviewing documented guidelines on running and managing clinical trials as well as getting individuals involved in the management of clinical trials to complete an online survey. The findings from this study will help in the improvement of BRM processes in clinical trials or serve as a guideline on how BRM can be incorporated into current management practices of clinical trials.

1.2 Background

Clinical trials are set up to test and collect data on experimental interventions such as new vaccines, drugs or therapies (Mahan, 2014; Ioannidis, 2016). The central objectives of clinical research is to develop generalizable knowledge and to improve and understand human health (Emanuel, 2000). To determine whether an intervention would be beneficial or detrimental to humans, clinical trials of one intervention are broken into several sequential phases with each phase meant to achieve a specific purpose in the testing of the unproven intervention (Mahan, 2014).

1.2.1 Clinical Trials

A number of clinical trial phases are used to establish the effectiveness and safety of new interventions (Mahan, 2014; Ioannidis, 2016). Clinical trials can only be carried out after successful pre-clinical studies that tested the intervention in laboratories and on non-humans for efficacy, toxicities and pharmacokinetics (Mahan, 2014). One intervention has to be tested through five phases that require human participants with each phase testing a separate aspect of the intervention (Umscheid *et al.*, 2011; Mahan, 2014). Phase I trials evaluate the safety and the best way to administer the treatment (Ross, 2006; Umscheid *et al.*, 2011; Mahan, 2014). Phase II trials test the efficacy and effectiveness of the interventions with one group getting a placebo and another group getting the real intervention, that is demonstrate the 'clinical promise' (Umscheid *et al.*, 2011; Mahan, 2014). Detailed understanding of the effectiveness of the treatment is established in Phase III trials also known as the "pre-marketing phase" of clinical trials (Mahan, 2014). When all goes well in Phase III, Phase IV trials are then conducted to establish the practicality of long-term usage in a "real world" setting (Umscheid *et al.*, 2011; Mahan, 2014). Once approved, the main focus of the final Phase of trials, Phase V trials, is to determine integration of a new therapy into wide spread clinical practice (Mahan, 2014).It is only when phases I-IV have been completed and analyzed successfully that the intervention be licensed (Mahan, 2014).

There are ethical requirements because human beings are used as subjects (Emanuel, 2000). Emanuel (2000) described seven ethical requirements of clinical research that are universal and must be adapted in all aspects of clinical research. One of the key requirements is that the research must be valuable and that there must be enhancements of health or knowledge derived from the research (Emanuel, 2000). Another ethical requirement mentioned by Emanuel (2000) that complements the derived value, is that the research must have an acceptable risk-benefit profile. Within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks (Emanuel, 2000).

There are existing guidelines and bodies that aim to promote efficient and ethical management of clinical trials. These include, but are not limited to, Good clinical practice (GCP) guidelines, guidelines from the Declaration of Helsinki and organizations such as the Food and Drug Administration (FDA) (Otte *et al.*, 2005). Investigators and research institutions such as universities and pharmaceutical companies, with the involvement of Institutional Review Boards (IRB) and Research Ethics Committees (RECs) all have specific roles in clinical research projects as a way to deliver impactful outcomes and add value to society as whole (Rid and Wendler, 2011).

However, studies have shown inadequacies in how some clinical trials are conducted, managed and reported (Smyth *et al.*, 2015). There are challenges in measuring outcome variables and adhering to protocols (Smyth *et al.*, 2015). Waste across medical research (clinical or other types) has been estimated as consuming 85% of the billions spent in those areas each year (Macleod *et al.*, 2014). It is estimated that about 1 million papers from clinical trials have been published to date, along with tens of thousands of systematic reviews (Ioannidis, 2016). Most of these papers have been deemed to be not very useful (Borgerson, 2016; Ioannidis, 2016).

There is a consensus that the approach to running clinical trials requires adjustment (Macleod *et al.*, 2014; Borgerson, 2016; Ioannidis, 2016). Complexity is central to management of clinical trials as there are multiple functions and aspects to manage. Complexity in management is a result of

sizeable projects that have a high degree of uncertainty, have numerous interacting elements and apply new methods (Vidal and Marle, 2008). In clinical trials, the complexity can come from the planning and design, funding, authorization, operating within regulations, monitoring and evaluation, public health implications to project management processes, project success factors, risk and close outs (Bossert *et al.*, 2002). It is however still important that during the life cycle of the clinical research projects; the planned benefits are still managed regardless of the complexity.

1.2.2 Benefits management

If a project is adequately designed and managed, its impact should always be equal to its potential at the start (Hubbard, 2000). To realize the full potential of a project, it is important to monitor and evaluate its performance as a way to increase the value and trace reasons for any shortcomings (Hubbard, 2000). When designing a project plan, focus should be placed on the connection between project goals and the purpose behind those goals (Figure 1). An efficiently managed project will produce the desired outputs, the desired output will fulfil the purpose and the project goals will be met (Hubbard, 2000).

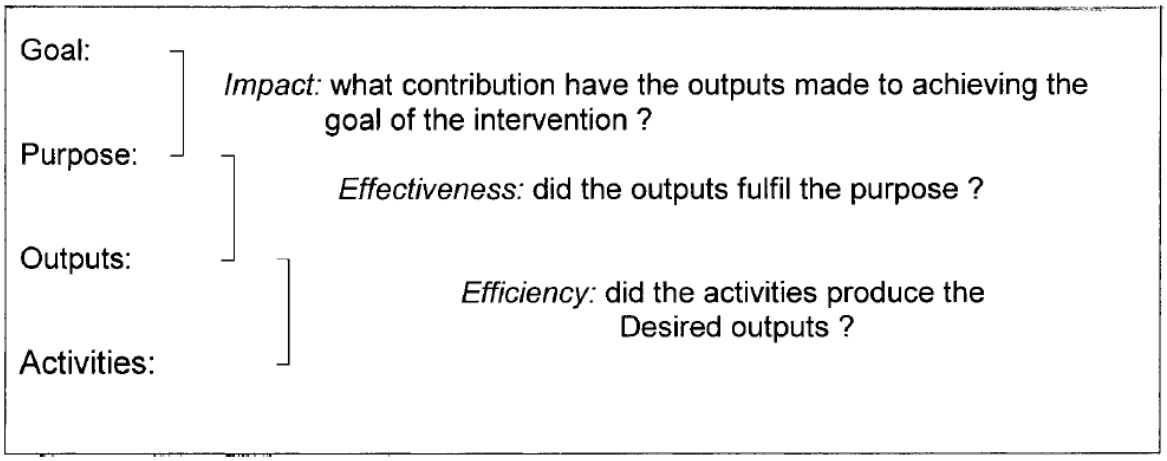

Figure 1 Logical Framework used by the European Commission to evaluate efficiency, effectiveness and impact (adopted from Hubbard 2000).

King (2000) states that there must be a reasonable chance of direct benefit from an intervention being studied before the possibility of direct benefit may be offered to potential subjects.

Without clinical trials, there is limited evidence that the experimental intervention is fully beneficial and the trials are a way of gathering more evidence (King, 2000). Research is however, a tool to investigate the unknown and the outcomes are uncertain (Emanuel, 2000). This uncertainty means that a clinical trial that is efficiently managed may still not produce the desired outputs and therefore not fulfil the purpose (Farrell, 1998; Farrell *et al.*, 2010). It is therefore hard to make any promises or give any guarantees on how efficient the intervention is and how long it will remain efficient without overselling through optimism bias (Chalmers and Matthews, 2006).

In most of the literature, there are three "agreed on" key types of benefits that have been described where clinical trials are concerned (King, 2000; Ross, 2006; Koonrungsesomboon *et al.*, 2016). These are:

1. Direct benefits to subjects: benefits that arise from receiving the intervention being studied.
2. Collateral benefits to subjects: benefits that arise from being a subject, even if one does not receive the experimental intervention. For instance, these could be a free physical exam or free medical care.
3. Aspiration benefits to society and future patients: these arise from the results of the study (King, 2000; Ross, 2006; Koonrungsesomboon *et al.*, 2016).

Due to the uncertainty of clinical trials, it is hard to make any guarantees on benefits (King, 2000). In the end, consent forms for participants in clinical trials will have strong legally tight statements to protect the stakeholders against unrealistic benefit expectations. Statements such as:

> *"A reasonable chance of direct benefit exists when a reasonable person under all the circumstances would consider the nature, magnitude, and likelihood of direct benefit sufficient to reasonably choose to participate in research in anticipation of the benefit"*

> *"The prospect of direct benefit may be too small, too attenuated, too unlikely, too uncertain to hold out as reasonable to expect."*

"It is not known whether your participation in this research study will have a beneficial effect."

"We do not know if the benefit will occur or for how long any benefit will last" (King, 2000).

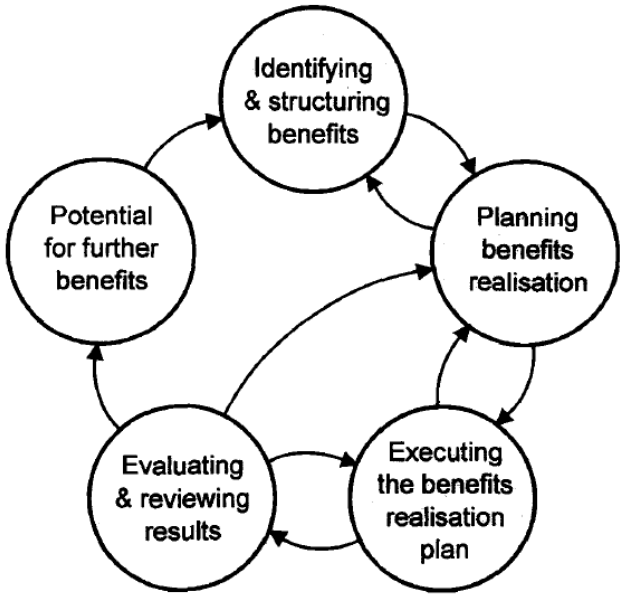

Figure 2 The Cranfield Process Model for benefits management (adapted from (Ward *et al.*, 1996)).

In this work, benefit will be defined as the improvement resulting from a change (outcome) that is perceived as positive by one or more stakeholders (Laursen and Svejvig, 2016). The benefits of clinical trials can be measured in terms of lives saved, life years gained or improvements in quality of life (Detsky, 1989). With uncertainty around delivering clinical trial benefits, it is worth looking into the management processes of benefits in clinical trials. In most Information Technology (IT) and Information Systems (IS) projects, benefits realization management (BRM) is used to deliver potentials benefits (Lin and Pervan, 2003; Badewi, 2016). In IT/IS projects, BRM is defined as the process of organizing and managing such that potential benefits arising from the use of IT/IS, are actually realized (Ward *et al.*, 1996). BRM ensures that project and programs deliver what they promised (Esteves and Dwivedi, 2009). It provides focus, reduces risk of failure and maximizes benefits achieved (Esteves and Dwivedi, 2009). Lin and Pervan (2003) highlight the usefulness of applying formal BRM methodologies and reviews and that different people need to be allocated BRM responsibility.

The Cranfield process model in figure 2, is commonly used in projects for delivering benefits (Ward *et al.*, 1996; Lin and Pervan, 2003). It is also used for remedial action to obtain benefits that are being lost, and, in most cases, for identification of further benefits that could be uncovered as the project is running (Lin and Pervan, 2003).The model in figure 2 describes the five different stages of managing benefits. The first stage is the identification and structuring of benefits. This involves the listing and detailing of all project benefits and aligning them with outcomes and therefore, strategic goals (Ward *et al.*, 1996; Serra and Kunc, 2015).

Once the benefits are identified and described, the second stage of the model is the planning (Ward *et al.*, 1996). A benefit realization approach requires careful planning and management (Ward *et al.*, 1996). The planning focuses on the changes that will lead to the desired outcomes and these have to be described and documented (Serra and Kunc, 2015). The BRM processes and approach have to be integrated with other branches of management for a holistic approach (Ward *et al.*, 1996; Lin and Pervan, 2003; Ashurst *et al.*, 2008; Serra and Kunc, 2015).

The third stage of the model focuses on the delivery of Benefits (Ward *et al.*, 1996). Benefits are not automatic thus the design of the benefits realization plan and executing it will lead to the realization of the identified benefits (Ward *et al.*, 1996; Ashurst *et al.*, 2008). It is the implementation of the changes that will bring about the benefits (Ward *et al.*, 1996; Laursen and Svejvig, 2016).

The fourth stage of the model incorporates the systematic reviewing and measuring of benefits (Ward *et al.*, 1996; Ashurst *et al.*, 2008). The benefits review stage is essential because benefits change over the course of the project and have to be reviewed and updated (Ashurst *et al.*, 2008). Benefits have to be measured to show added value and intermediate benefits (Ward *et al.*, 1996; Ashurst *et al.*, 2008).

The final stage of the model focuses on further benefits exploration and application of lessons learned in the exploration stage (Ward *et al.*, 1996). This involves the adoption of practices

required to realize the potential benefits from available information based on the organizational learning through monitoring and evaluation of benefits (Ward *et al.*, 1996; Ashurst *et al.*, 2008). There is a connection between BRM processes and strategy and the management approach as shown in figure 3 (Mossalam and Arafa, 2016).

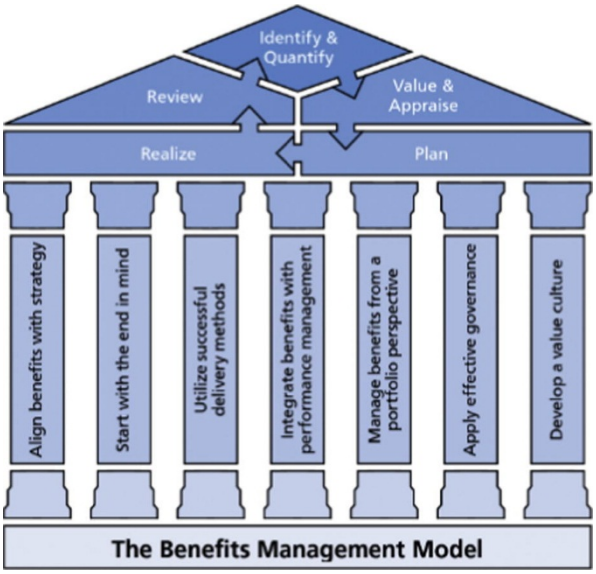

Figure 3 Critical Success Factors for Benefits management (adapted from (Mossalam and Arafa, 2016).

For the BRM processes in figure 2 to be successful, they have to be placed on the seven "pillars" of BRM as shown in figure 3. The "pillars" include:

- Aligning benefits with strategy;
- Starting with the end of the project in mind;
- Utilizing successful delivery methods;
- Integrating benefits with performance management;
- Managing benefits from a portfolio perspective;
- Applying effective governance;
- And developing a value culture (Mossalam and Arafa, 2016).

At the project level, Mossalam and Arafa (2016) proposed a merge of the BRM processes into all the project management processes as shown in figure 4. These are included in the lifecycle of the project from initiation to the closeout. The updated processes further extend into the

implementation phase to include benefits transition and sustainability (Mossalam and Arafa, 2016).

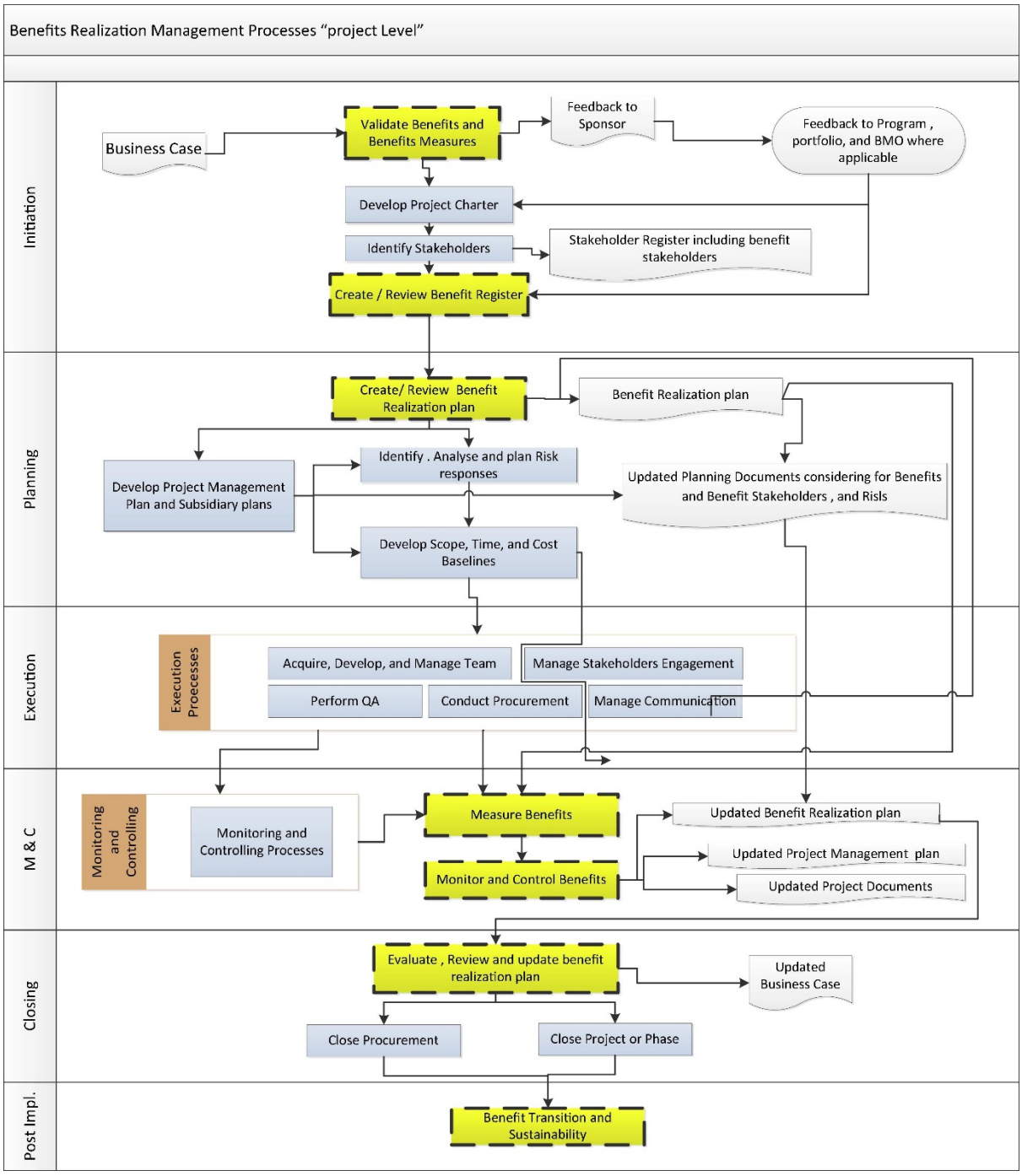

Figure 4 Updated project management processes that include BRM processes as proposed by Mossalam and Arafa (2016).

1.2.3 Proposed Research Subject

HIV clinical trials consist multi-disciplinary collaboration of scientists, educators and community members (Kublin *et al.*, 2012; HVTN, 2017). The aim of most clinical trials is to enhance the discovery and facilitate the development of a safe and globally effective intervention to prevent, treat or cure HIV/AIDS.

1.3 Rational for the research

Africa is one of the centres for setting up of clinical trial sites, these trials are expensive and without guarantees. It is important that these clinical trials yield useful and applicable results not only because of the need for an HIV vaccine but also because of the risk taken by the participants and volunteers. Trial managers and researchers must therefore increase the chances of successful outcomes by using tools that will lead to realizing and sustaining planned benefits of clinical trials. Macleod *et al.* (2014) and (Borgerson, 2016) point out that alternative approaches to clinical trials are necessary to limit waste and to improve impacts. There is a lack of clear guidelines on how to achieve the effectiveness or benefits derived from clinical trials of a new therapy or intervention. Benefits must still be managed regardless of the uncertainty of their delivery. It is therefore worth exploring BRM processes in clinical trials as a means to increasing the likelihood of benefits realization.

1.4 Problem statement

There is an emphasis in clinical trials literature that clinical trial benefits must always outweigh the risks yet there is limited clarity on processes to manage and ensure benefits delivery.

1.5 Research Questions

The main question to address the problem statement above is:

- Are there comprehensive benefits management processes in HIV clinical trials?

The sub-questions are:

- What are the current benefit management practices in HIV clinical trials?
- How do the current clinical trials practices compare with those described in the literature?

1.6 Aim

To explore the current processes used to manage and deliver benefits in clinical trials in spite of the uncertainty around the outcomes of clinical research.

1.7 Objectives

To achieve the above aim, the objectives of this study are as follows:

- Establish the existence or absence of benefits management processes in HIV clinical trials.
- Compare the HIV clinical trials BRM processes with BRM processes in the literature.
- Propose improvements depending of existing processes by designing a concept model

1.8 Research Design and Methods

To gain an insight into the practice of benefits management in clinical trials, an inductive research study explored BRM and BRM processes in clinical trials. The study will be in two parts with the first part being a search for specific BRM processes in current guidelines of how to manage clinical trials. The second part of the study will be an assessment of BRM processes in practice through online questionnaires with individuals that hold management positions in different clinical trials. The two parts will therefore evaluate the regularity of application of BRM and the perception of its efficiency. This will be a qualitative study so once the data has been gathered, the qualitative data will be recorded in a coded manner that enables analysis with programs such as SPSS.

1.9 Limitations

Literature available on BRM is mostly on benefits in the IT/IS industry (Ward *et al.*, 1996; Lin and Pervan, 2003; Love and Irani, 2004; Love *et al.*, 2005; Ashurst *et al.*, 2008). There is a chance that

the BRM processes in literature are IT/IS specific and may not be applicable in clinical research projects. There is also a possibility that there is limited reporting of existing BRM in clinical trials. Privacy policies may restrict access to clinical trial documents and specific guidelines. Another challenge will be accessing the clinical trial stakeholders to participate due to the geographical distribution of the different clinical sites and research institutions. The number of people that will respond to the questionnaire will be low and should ideally be higher for a more significant and complete assessment and obtaining those high numbers will be challenging.

1.10 Resources and costs

At this time, there are no foreseeable costs that this project will require. The plan is to use the literature databases that the university has access to for all the literature needs. For data analysis, the plan is to use the available software also provided for by the university with paid for licenses.

2 Literature Review

2.1 Overview

This chapter is a review of the relevant literature to the research topic and provides context to the research problem. The review will begin with an introduction into clinical trials and health research projects. The sections that follow will focus on the general management of clinical trials as well as project management practices in clinical trials. This will lead into the final section which will review published work on general benefits realization management and link that with management practices in clinical research.

2.2 Clinical trials

2.2.1 What are clinical trials?

Disease and human beings have always coexisted. Human beings have always been hunting for better ways to fight diseases be it through medicine, hygiene or diet. As newer and deadlier diseases emerge, human beings have to come up with interventions to combat these diseases. One of the tools used in the fight against diseases is clinical research and clinical trials. A clinical trial is a prospective study which compares the effect of an intervention with a control (Chew, 2011). Clinical trials are set up to test and collect data on experimental interventions such as new vaccines, drugs, treatment strategy or therapies (Chew, 2011; Mahan, 2014; Ioannidis, 2016).

The world cannot afford to not have clinical trials because the clinical trial results may help change current patient care practices and have an impact on community (Chew, 2011; Aghayan *et al.*, 2014). Clinical trials are the gold standard for evaluating therapies, providing the highest evidence for the practice of evidence-based medicine and health care reform (Chew, 2011; Umscheid *et al.*, 2011; Aghayan *et al.*, 2014). Clinical research is useful for discovering the truth and developing generalizable knowledge (Farrell, 1998; Emanuel, 2000; Casarett *et al.*, 2002; Chew, 2011). The results can change medical dogmas and/or retire widely accepted therapies

that have little or no efficacy this way saving both patient lives and eliminating unnecessary costs (Farrell, 1998; Emanuel, 2000; Casarett *et al.*, 2002; Chew, 2011).

2.2.2 The structure of clinical trials

To determine if an intervention would be beneficial or detrimental to humans, clinical trials of one intervention are broken into several sequential phases as shown in figure 5 with each phase meant to achieve a specific purpose in the testing of the unproven intervention (Mahan, 2014).

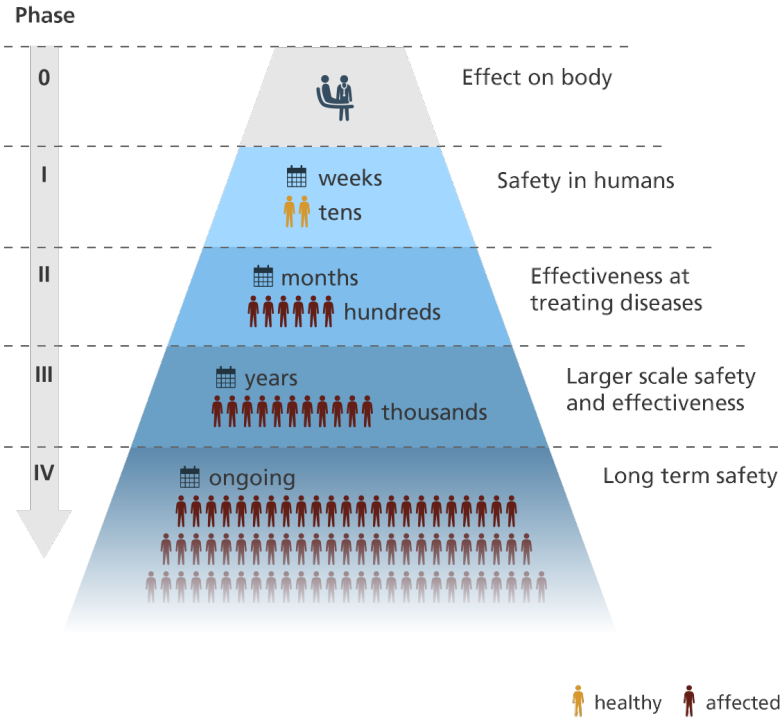

Figure 5 Different phases of clinical trials (Courtesy of (Your Genome, 2017).

Pre-clinical studies and Phase 0 clinical trials: are focused on testing the intervention in non-humans for efficacy, toxicities, pharmacokinetics (Umscheid *et al.*, 2011; Mahan, 2014). Phase I is the first of the phases that involve human participants. Phase I trials evaluate the safety and the best way to administer the treatment (Mahan, 2014). Phase II trials test the efficacy and effectiveness of the interventions with one group getting a placebo and another group getting the real intervention. The point is to demonstrate the 'clinical promise' (Umscheid *et al.*, 2011; Mahan, 2014). Phase III trials are meant to give detailed understanding of the effectiveness of

the treatment. This is the "pre-marketing phase" of clinical trials (Umscheid *et al.*, 2011; Mahan, 2014). Phase IV trials are useful for establishing the practicality of long-term usage in a "real world" setting (Umscheid *et al.*, 2011; Mahan, 2014).

Once the intervention is approved, Phase V trials focus on determining the integration of a new therapy into wide spread clinical practice (Mahan, 2014). Throughout each phase, the participants are randomized to reduce treater-selection bias and for statistical analyses (Chew, 2011).

2.2.3 What constitutes a good clinical trial?

2.2.3.1 Ethical requirements

A clinical trial that meets all ethical requirements and expectation is a good clinical trial. According to Emanuel (2000), there are seven key universal requirements that clinical research studies must meet to be regarded as ethical. These are:

(1) The research must add *value* by enhancements of health or knowledge.
(2) The research must have *scientific validity.*
(3) The must be *fair selection* of study sites and the inclusion criteria for individual subjects must be fair.
(4) The *risk-benefit ratio must always be favorable*. This means that the risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks.
(5) There should be an *independent review* of the research by unaffiliated individuals.
(6) There should always be *Informed consent* by individuals who will participate in the research; and
(7) There enrolled subjects should be r*espected*, their privacy protected, given the opportunity to withdraw, and their well-being monitored (Emanuel, 2000).

Other long recognized fundamental values of clinical research are nonmaleficence and beneficence and they ensure a favorable risk-benefit ratio (Emanuel, 2000). Beneficence as articulated by the National Commission for the Protection of Human Subjects in Biomedical and

Behavioural Research (1979) in the Belmont Report, is to maximize possible benefits and to minimize possible harms (Emanuel, 2000; Rid *et al.*, 2010; Grankvist and Kimmelman, 2016; Koonrungsesomboon *et al.*, 2016; Resnik, 2017). The principle of nonmaleficence states that one ought not to inflict harm on a person in the pursuit of benefits (Emanuel, 2000). This justifies the need to reasonably reduce the risks associated with clinical research (Emanuel, 2000). It would be pointless and unethical to continue with a clinical trial that carries more risks than benefits.

Equipoise is a key ethical concept and requirement for randomized clinical trials which are great tools for providing impartial evidence (Rabinstein *et al.*, 2016; Braakhekke *et al.*, 2017). Equipoise is a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits between Treatment A and Treatment B in population P (Freedman, 1987; Rabinstein *et al.*, 2016; Braakhekke *et al.*, 2017). This requirement entails that the investigator must have no "treatment preference" throughout the course of the clinical trial (Freedman, 1987). A randomised clinical trial can only continue if and only if, there are unknowns about how new Treatment B compares to Treatment A (Freedman, 1987; Rabinstein *et al.*, 2016). Should the investigator discover that one treatment is of superior therapeutic merit, he or she is ethically obliged to offer that treatment (Freedman, 1987).

If equipoise is disturbed during the trial, the trial should be stopped (Freedman, 1987). Equipoise is disturbed if:

- Biological plausibility is known : if treatment is known to work, it is unethical to test it (Braakhekke *et al.*, 2017)
- Biological plausibility is absent : When it is known that it will not work (Braakhekke *et al.*, 2017)
- Biological plausibility is uncertain : No basis to test it, inconclusive multiple preliminary results (Braakhekke *et al.*, 2017).

2.2.3.2 Generalizability

A good clinical trial is one that is well designed and has a solid scientific/clinical question that is being investigated (Farrell *et al.*, 2010). Plans, systems, and procedures have to be in place and followed on a day to day basis to ensure the delivery of the desired outcome (Farrell, 1998).

It is important to highlight that biased or inaccurate knowledge extracted from flawed clinical trials may lead to the inadvertent harm of patients (Chew, 2011; Umscheid *et al.*, 2011). It is because of this potential impact of clinical trials that clinical trials are well managed and controlled. Once completed, it is important that the findings of the research are disseminated and where applicable, incorporated into clinical practice (Farrell *et al.*, 2010). Results of a trial can be made widely available using a variety of media, such as articles in medical journals, online journals, trial registers, systematic reviews and conference presentations (Farrell *et al.*, 2010). The ideal clinical trial yields findings that are applicable to clinical practice in the "real world" (Umscheid *et al.*, 2011). This is known as generalizability or external validity (Umscheid *et al.*, 2011).

It is also important to sell the clinical trial to the public as these are the people that will volunteer into the trial and stand to benefit from it. A marketing approach has to be taken and applied to clinical trials as they have to be treated like commodities to manage and sell so that different stakeholders will want to participate (Francis *et al.*, 2007; Farrell *et al.*, 2010). It is important that communication channels are well set up and utilized with the many stakeholders involved in clinical trials (Farrell, 1998).

2.2.4 What are the roles of those in clinical research?

All clinical research and randomized clinical trials require multiple experts from different fields such as statisticians and clinicians to work together to design the best possible trial to address the research question (Chew, 2011). A typical clinical trial consists of:

- A principal investigator: This is the overall leader that designs and directs the clinical trial in order to achieve set goals. The overall responsibility for delivering the trial lies with the principal investigator (Goodarzynejad and Babamahmoodi, 2015).
- The trial manager is responsible for day to day issues of clinical trial sites, the personnel and the workflow of the trial (Goodarzynejad and Babamahmoodi, 2015). Trial managers are responsible for ensuring that all aspects of the project are planned, implemented, monitored, and controlled on a daily basis, and that the project outputs and outcomes are obtained (Goodarzynejad and Babamahmoodi, 2015). This includes areas such as marketing, finance, staff issues, data collection, enrolment and development of the trial (Farrell, 1998). Ideally, trial managers should be involved early on in the trial design phase, but this is rarely possible because of funding constraints (Farrell *et al.*, 2010).
- The clinical project manager is a professional who contributes project management practices to the clinical research to ensure that all stages of a clinical trial are properly managed. The project manager ensures that the objectives of the trial are achieved on time, on budget, and according to the GCP, and that the safety of the subjects participating in the clinical trial and the quality of collected data are guaranteed (Goodarzynejad and Babamahmoodi, 2015).
- Trial Statistician provides a statistical input in the design and the data analysis (Farrell, 1998).
- Trial secretary is in charge of key correspondence (Farrell, 1998).
- There are many other role players in clinical trials such as the data manager, the data collectors, nurses and clinicians that responsible for collecting samples and conduct health checks on the clinical participants.

2.2.5 Who are the beneficiaries?

Patients, health care providers and the pharmaceutical industry can reap maximum benefits from effectively conducted clinical trials (Umscheid *et al.*, 2011). Clinical trials for disease prevention often enrol a part of the population at the highest risk of developing the disease and clinical trials for a therapeutic intervention targets the population with the highest risk of progressing to a more severe stage of the disease (Chew, 2011). It is these populations that stand the biggest chance of benefiting from the intervention when the intervention is shown to be effective and is

eventually licensed. Overall, successful clinical trials are a useful tool for combating diseases and the general public stands to benefit from resulting disease cure and/or prevention interventions that results.

2.3 HIV Clinical Trials

Due to the devastating effects of HIV/AIDS on people all over the world in recent years, there have been many coordinated collaborative efforts to battle the disease. These come in all forms from scientists looking for either a vaccine or the cure to those that promote awareness and invent treatment regimens. An example of such a network of scientist is the HIV Vaccine Trials Network (HVTN). The HVTN is an international group that coordinates collaboration of scientists, educators and community members (Kublin *et al.*, 2012; HVTN, 2017). The HVTN focuses on the discovery and development of a safe and globally effective HIV/AIDS vaccine (Kublin *et al.*, 2012; HVTN, 2017). Funding is provided by public and private sources such as the U.S. National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation (HVTN, 2017).

The HVTN conducts all phases of clinical trials to evaluate experimental vaccines for safety and immunogenicity as well as testing vaccine efficacy (HVTN, 2017). The network's clinical research sites are located at leading research institutions in over 30 cities on five continents and this result in engaging with communities and internationally renowned researchers in HIV vaccines and prevention (HVTN, 2017). One of the main HVTN trials that is currently taking place in South Africa is the HVTN 702 which is a phase 3 HIV vaccine efficacy trial (HVTN, 2017). HVTN 702 evaluates a new version of the only HIV vaccine candidate to have shown some protection against HIV especially against HIV subtype that is predominant in southern Africa (HVTN, 2017).

Since its creation in 1999, the HVTN has conducted over 50 clinical trials and results related to HVTN studies have been published in more than 300 manuscripts in peer-reviewed scientific journals (Kublin *et al.*, 2012; HVTN, 2017). Collaborative HVTN projects have outcomes that have altered the vaccine design and development field moving forward (HVTN, 2017). The HVTN has successfully streamlined protocol development and established standardized methodologies and

systems allowing for reliable assessments standards across trials (Kublin *et al.*, 2012; HVTN, 2017). Over the past decade, the HVTN has aimed to improve the process of designing, implementing, and analyzing vaccine trials (HVTN, 2017).

2.4 Management in clinical trials

Clinical trials require coordinated processes and systems regardless of their size, scope, costs, or period (Goodarzynejad and Babamahmoodi, 2015). A clinical trial requires huge investments of time, money and people (Farrell *et al.*, 2010). This means expert management is needed for clinical trials just like in any other business (Farrell *et al.*, 2010). Clinical trials have many characteristics in common with other types of business projects. To bring about change using specified resources, a clinical trial like any business project has pre-defined objectives, a beginning and an end. All key activities are planned and executed by a team with constant monitoring and evaluation (Farrell *et al.*, 2010). A list of all the key activities of a clinical trial are shown in appendix C.

2.4.1 Project management in clinical trials

"A guide to project management body of knowledge: PMBOK guide (PMBOK)" contains a compilation of guidelines on project management that are published by the project management institute (PMI, 2013). The PMBOK defines project management as 'the application of knowledge, skills, tools, techniques to a broad range of activities in order to meet requirements of a particular project'(PMI, 2013). Project management is used by the military, in engineering, commerce, industry, information systems, financial services, education and training, and health services (Payne *et al.*, 2011).

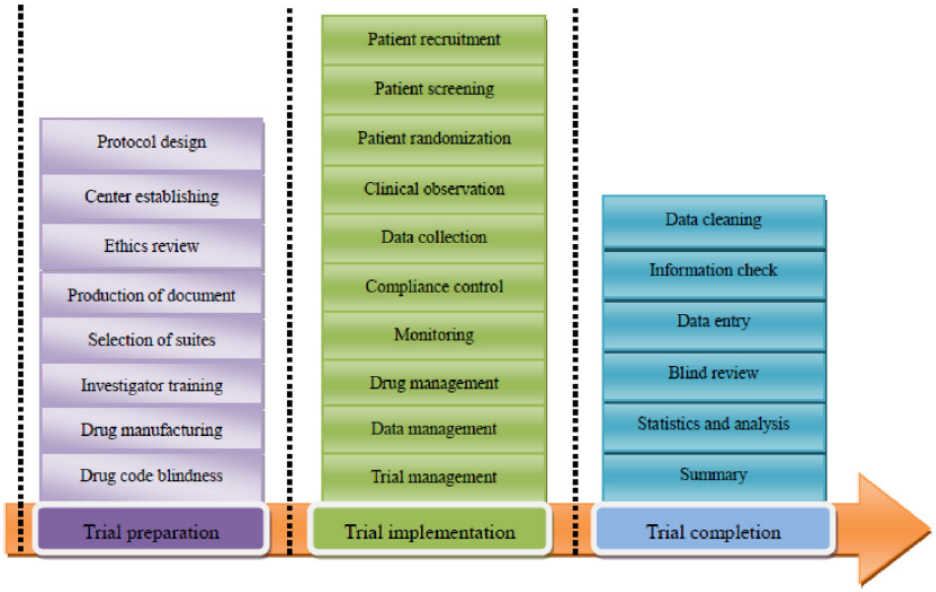

Figure 6 Clinical Trial flow Process (Cao *et al.*, 2013)

There are those who have highlighted the need and application of project management in clinical research (Payne *et al.*, 2011; Aghayan *et al.*, 2014; Goodarzynejad and Babamahmoodi, 2015). Research is a project that can be defined as a unique and scheduled complex attempt to achieve specific and predefined objectives by using limited budget and resources which is usually no repetitive within an organization (Aghayan *et al.*, 2014). Figure 6 shows a summary of the key areas that management focuses on during clinical trials (Cao *et al.*, 2013). Trial preparation involves all the planning and prerequisites that need to be arranged before the clinical trial can resume. Recruitment of trial participants following pre-set conditions of acceptance and rejection, is one of the first steps in the implementation of the clinical trial (WHO, 2005). Once the tests and sample collections are completed, the data are analyzed and then a summary and reports are compiled to bring the trial to completion.

Project management may benefit both the managerial and scientific aspects of medical projects and reduce fund waste. However, little has been written to date on project management in the context of clinical research (Goodarzynejad and Babamahmoodi, 2015). Like most projects, aspects of clinical research projects can fit the five basic processes of the project life cycle:

2.4.1.1 Initiating

The main focus at this stage of a clinical trial management is on the protocol design and the rationale behind the trial. This is where clear objectives and aims of the trial and its specific outputs are defined and formulated (Aghayan *et al.*, 2014). The key investigator will offer background information on the intervention (Goodarzynejad and Babamahmoodi, 2015). The trial has to meet all the ethical requirements set by regulatory bodies such as the IRB (Chew, 2011). Each trial needs to develop a management blueprint setting achievable targets, developing an enthusiastic team and securing the time and money to make the whole process efficient and deliverable (Farrell, 1998).

2.4.1.2 Planning

The project plan should also describe what the stakeholders of the trial are trying to achieve, planned processes, how resources will be used and within what time frame (Farrell *et al.*, 2010). Figure 7 shows a progress layout of a clinical trial through the enrolment, allocation, post-allocation and close-out phases. A team with requisite knowledge and skills is organized and the project plan should describe who will be responsible for essential activities, communication with the collaborative group, recruitment monitoring, data management, and raising project awareness (promotion/marketing), through to safety reporting, analysis, report writing and dissemination of the trial results (Farrell *et al.*, 2010; Aghayan *et al.*, 2014). A risk management plan has to be part of the planning.

2.4.1.3 Executing

One of the first acts in clinical trials is the recruitment of appropriate patient/participants into the study (Umscheid *et al.*, 2011). The participants are screened, randomly allocated to separate groups of the study depending on the study design (Schulz *et al.*, 2010). The intervention can be distributed or tested on different groups with dosage or any other changes being done accordingly as this process continues (Goodarzynejad and Babamahmoodi, 2015). The clinical observation and data collection then begins. The day to day matters of the trial are heavily managed at this point by the trial manager (Goodarzynejad and Babamahmoodi, 2015).

	Study Period							
	Enrollment	Allocation	Postallocation					Closeout
Time point*	$-t_1$	0	t_1	t_2	t_3	t_4	etc.	t_x
Enrollment:								
Eligibility screen	X							
Informed consent	X							
[List other procedures]	X							
Allocation		X						
Interventions:								
[Intervention A]			◆	—	◆			
[Intervention B]			X		X			
[List other study groups]			◆	—	—	◆		
Assessments:								
[List baseline variables]	X	X						
[List outcome variables]				X		X	etc.	X
[List other data variables]			X	X	X	X	etc.	X

Figure 7 Flow diagram of the progress through the phase of a parallel randomised trial as adopted from (Chan *et al.*, 2013).

2.4.1.4 Monitoring and controlling

Constantly reviewing and adapting the project plan is crucial as a trial can be hit side-on by events outside its control. Sensible risk assessment, tailored quality assurance management systems and real-time monitoring are essential if a trial is to optimize its potential and provide reliable evidence (Farrell *et al.*, 2010). The Data and Safety Monitoring Committee (DSMC) are individuals with varying expertise including statisticians, clinicians and clinical trialists charged with ensuring the safety of the participants by periodic evaluation of the data (Chew, 2011). They will also evaluate baseline variables, adverse effects, and response to therapy periodically (Chew, 2011). The DSMC makes recommendations to the study leadership for early termination of the study of there is unanticipated serious toxicity, greater than the expected benefits, or the likelihood of not finding a difference between the treatment and control group (Chew, 2011).

2.4.1.5 Closure

The trial enters the closure phase when the findings are analyzed and reported. The data is “un-blinded” by revealing the participants that were randomly assigned and statistically analyzed to

compare the effects of those who received the intervention versus those who did not (Schulz *et al.*, 2010). All the data and information collected is checked and queries addressed (Goodarzynejad and Babamahmoodi, 2015). The project is closed when the objectives have been achieved or when the objectives will not or cannot be met, or when the need for the project no longer exists(Farrell *et al.*, 2010; Goodarzynejad and Babamahmoodi, 2015). The findings and summary of the clinical trial can then be reported as directed by the CONSORT 2010 guidelines (Schulz *et al.*, 2010; Umscheid *et al.*, 2011).

2.4.2 Clinical Trial Management

The management approach of clinical trials is not like that of standard business projects. The management approach is shaped and guided by set standards of several regulatory bodies. These industry "watchdogs" regulate and audit clinical trials from beginning to end and therefore shape how clinical trials are managed. These are some of the regulatory clinical trial bodies and practices:

2.4.2.1 Good Clinical Practice (GCP)

Management approach of clinical trials is mainly shaped by Good Clinical Practice (GCP) guidelines. GCP standards are used internationally to set the bar for ethical and scientific quality (Otte *et al.*, 2005; Bongiovanni *et al.*, 2015). Clinical researchers have to take GCP guideline when designing, conducting and reporting trials that involve the participation of human subjects (Otte *et al.*, 2005; Bongiovanni *et al.*, 2015). GCP was born due to the concerns that came about when human subjects started being used in medical research in the 1900s (Otte *et al.*, 2005). These Guidelines have taken many forms an included many organizations over the years with necessary changes being added as necessary as shown in figure 8 (Otte *et al.*, 2005).

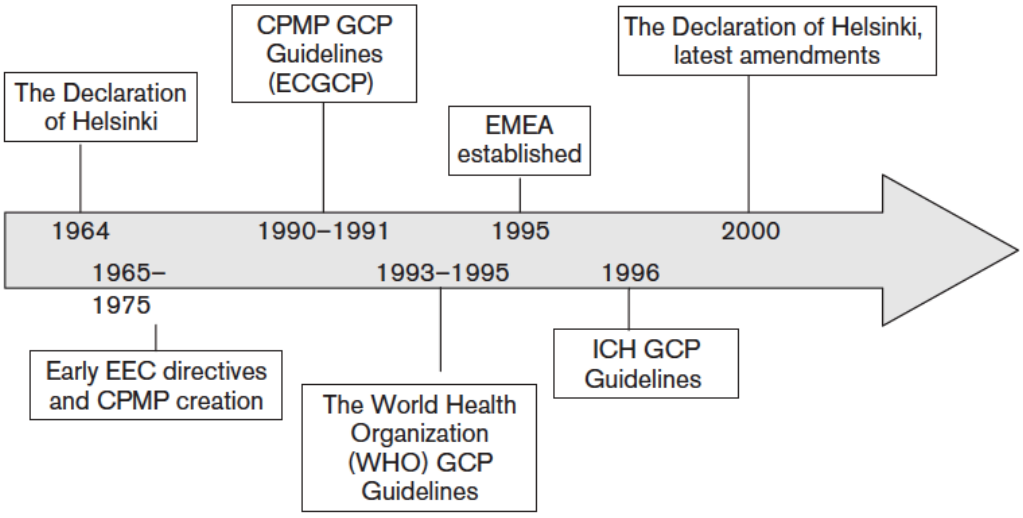

Figure 8 Milestones in the international development of good clinical practice (Otte *et al.*, 2005).

The key aspects of GCP is to:

- protect the rights, safety, and well-being of trial subjects;
- ensure the quality and integrity of data obtained from clinical testing (Otte *et al.*, 2005).

The GCP guidelines informs researchers on many other components such as how to freely obtain informed consent from each subject, listing safety monitoring requirements, data handling and archiving requirements as well as outlining clinical trial responsibilities of the stakeholders (Otte *et al.*, 2005).

Otte *et al.* (2005) highlighted and summarized the 12 golden rules of GCP as follows:

1. Know and strictly follow the study protocol.
2. Select, train and keep a log of all study team members.
3. Record data correctly.
4. Ensure adequate study equipment.
5. Obtain ethics committee approval before starting and get the written informed consent of all subjects before they take part.
6. Predict recruitment accurately and keep an up-to-date subject enrolment log.
7. Precisely document product accountability.
8. Report serious adverse events immediately to the sponsor.

9. Check laboratory sample quality and review laboratory results.
10. Maintain good trial files and archives.
11. Diligently collect and record reliable data. Keep all source documents.
12. Keep everyone fully informed.

2.4.2.2 Institutional Review Boards (IRB)

One of the key elements of GCP is that medical researchers are only permitted to start a clinical trial if they obtained the approval of an Institutional Review Board (IRB) (Musschenga *et al.*, 2007; Chew, 2011). The IRB is made up of at least five members and this number usually included at least one member that has a non-scientific background and at least one member who is independent of the institution/trial site (Otte *et al.*, 2005). The IRB evaluate the scientific quality of a trial by reviewing its originality, importance, feasibility, methodological soundness and information provided to potential research subjects (Musschenga *et al.*, 2007). The IRB also review investigators capabilities and address relevant ethical concerns such as coercion or undue influence on the trial subjects (Otte *et al.*, 2005). Each trial must therefore be designed and managed to meet IRB applicable regulatory requirements.

2.4.2.3 Key documents

Clinical Trial Protocol - A protocol is a plan that details how a clinical trial is to be carried out and how the data are to be collected and analysed (Chow and Liu, 2008). A list of the key details that are included in a clinical trial protocol are shown in appendix D. A protocol ensures the quality and integrity of the clinical investigation in terms of its planning, execution, and conduct of the trial as well as the analysis of the data (Chow and Liu, 2008). A protocol provides details of the trial plans, rationale, ethics approval, administration of the trial, implementation, statistical analyses, dissemination of results, interpretation and external review (Chan *et al.*, 2013). The details in the protocol will influence how the report is written at all times (Al-Marzouki *et al.*, 2008).

Standard operating procedures (SOPs) – A SOP is a document of standardized working procedures for all functions (including the initiation, conduct, and reporting of clinical trials) implemented throughout the specific research unit organization in order to ensure accurate and reliable data

(Bairu and Chin, 2012). The concept of standardizing procedures (SOPs) was first developed in the manufacturing sector to ensure that products conform to specifications and standards and to eliminate batch to batch variability; it was later adopted by most industries (Bairu and Chin, 2012). SOPs are mandatory in all clinical research settings, including pharmaceutical companies, regulatory authorities, ethics committees and laboratories, (Bairu and Chin, 2012). SOPs assign responsibility to components of a process, SOPs act as step-by-step instructions for the training of new and temporary staff (Bairu and Chin, 2012).

Policies document the attitudes, norms, and expectations of an organization towards specific concepts, such as behaviour in the workplace, dress code and work-related travel (Bairu and Chin, 2012). Policies do not include procedures and do not necessarily assign responsibilities to specific positions (Bairu and Chin, 2012).

Guidelines are significantly more detailed than SOPs and are less stringently controlled. They are synonymous with regulations in a legal framework (Bairu and Chin, 2012). Guidelines contain wisdom that advises, in situations where prescribing is too restrictive (Bairu and Chin, 2012). An organization cannot be cited in an audit for not adhering to each element within a guideline (Bairu and Chin, 2012). Guidelines typically include details that improve quality but are not essential to meet regulatory requirements (Bairu and Chin, 2012).

2.4.2.4 Reporting

There are guidelines and requirements on the format and content of clinical trial reports and publications. This is to ensure that the reports cover all the key aspects of the clinical trial. There are several recommended formats for clinical trial publications but the most commonly used is the CONSORT Statement guidelines (Schulz *et al.*, 2010; Umscheid *et al.*, 2011). The CONSORT (Consolidated Standards of Reporting Trials) statement is a 25 items checklist guideline on information to include when reporting randomized controlled trials worldwide as shown on table 1 (Schulz *et al.*, 2010; Umscheid *et al.*, 2011). The CONSORT statement improves accessibility of clinical results to those in the position to use them (Schulz *et al.*, 2010; Umscheid *et al.*, 2011).

The CONSORT statement offers a layout that allows for an accurate assessment of a trial by readers of a published report as the report will be complete, clear, and transparent information on its methodology and findings (Schulz *et al.*, 2010).

An alternative to the CONSORT statement is the SPIRIT Statement (Chan *et al.*, 2013). The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Statement is a 33-item checklist for all clinical trials that focuses on content rather than format (Chan *et al.*, 2013). The checklist recommends a full description of what is planned; it does not prescribe how to design or conduct a trial (Chan *et al.*, 2013). Adherence to SPIRIT enhances transparency and completeness of trial protocols for the benefit of investigators, trial participants, patients, sponsors, funders, research ethics committees or institutional review boards, peer reviewers, journals, trial registries, policymakers, regulators, and other key stakeholders (Chan *et al.*, 2013). There are a lot similarities between the SPIRIT Statement and the CONSORT Statement but their overall aim to promote diligent adherence by authors to the checklist items to facilitates clarity, completeness, and transparency of reporting (Schulz *et al.*, 2010).

2.4.2.5 Peer review

The established practice for evaluating science and research is through the peer review process (Barke, 2009). The peer review is done by experts and sometimes research committees (Barke, 2009). The US Department of Health and Human Services has stated that If data and analytic results have been subjected to formal, independent, external peer review, the information may generally be presumed to be of acceptable objectivity (Barke, 2009).

Table 1 CONSORT 2010 publication checklist Randomized Trial (Schulz *et al.*, 2010)

Section/Topic	Item	Checklist Item	Reported on Page No
Title and abstract	1a	Identification as a randomized trial in the title	----------
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	----------
Introduction	2a	Scientific background and explanation of **rationale**	----------
Background and objectives	2b	Specific **objectives** or hypotheses	----------
Methods			
Trial design	3a	Description of **trial design** (such as parallel, factorial) including allocation ratio	----------
	3b	Important **changes** to methods after trial commencement (such as eligibility criteria), with reasons	----------
Participants	4a	Eligibility criteria for participants	----------
	4b	**Settings and locations** where the data were collected	----------
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	----------
Outcomes	6a	Completely defined pre-specified primary and secondary **outcome measures**, including how and when they were assessed	----------
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	----------
	7b	When applicable, explanation of any interim analyses and stopping guidelines	----------
			----------
Randomization			
Sequence generation	8a	Method used to generate the random allocation sequence	----------
	8b	Type of randomization; details of any restriction (such as blocking and block size)	----------
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	----------
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	----------
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	----------
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	**Statistical methods** used to compare groups for primary and secondary outcomes	----------
	12b	Methods for **additional analyses**, such as subgroup analyses and adjusted analyses	----------
			----------
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the **numbers of participants** who were randomly assigned, received intended treatment, and were analysed for the primary outcome	----------
	13b	For each group, **losses and exclusions** after randomization, together with reasons	----------
Recruitment	14a	**Dates** defining the periods of recruitment and follow-up	----------
	14b	Why the **trial ended or was stopped**	----------
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	----------
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	----------
Outcomes and estimation	17a	For each primary and secondary outcome, **results** for each group, and the estimated effect size and its precision (such as 95% confidence interval)	----------
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	----------
Ancillary analyses	18	Results of any **other analyses** performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	----------
Harms	19	**All-important harms or unintended effects** in each group (for specific guidance see CONSORT for harms)	----------
Discussion			
Limitations	20	**Trial limitations**, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	----------
Generalizability	21	**Generalizability** (external validity, applicability) of the trial findings	----------
Interpretation	22	**Interpretation** consistent with results, balancing benefits and harms, and considering other relevant evidence	----------
Other information			
Registration	23	Registration number and name of trial registry	----------
Protocol	24	Where the full trial protocol can be accessed, if available	----------
Funding	25	Sources of **funding** and other support (such as supply of drugs), role of funders	----------

2.4.3 Limitations in Managing Clinical Trials

Managing clinical trials, of regardless of size requires efficient management (Farrell *et al.*, 2010). There are different categories of complexity that managers of clinical trials have to take into consideration. For this work, the CONSORT statement is used as a snapshot of the key areas of focus for management in clinical trials (highlighted in table 1). These important parts of the trial give rise to complexity. Complexity arises from recruiting large patient sample sizes, managing multisite teams, inclusion or exclusion criteria, scheduling, collaborations and the unpredictability of clinical outcomes (Bossert *et al.*, 2002). More of complexity in clinical research is due to the involvement of numerous stakeholders which include sponsors, scientists, staff, project managers, ethics committees, regulatory authorities, research subjects, and some others (Aghayan *et al.*, 2014). This is where project management tools become applicable and useful.

Many clinical trials fail to deliver because of the lack of a structured, practical, administrative and business-like approach to trial management (Farrell, 1998; Farrell *et al.*, 2010; Aghayan *et al.*, 2014). A sound scientific basis and a well-structured protocol can answer clinical questions but in the presence of inept management, successful delivery of a trial is unlikely (Farrell *et al.*, 2010; Goodarzynejad and Babamahmoodi, 2015). The GCP only controls and rules scientific experimentation, leaves unaddressed most management issues (Bongiovanni *et al.*, 2015). Most clinical researchers have limited training in project management (Payne *et al.*, 2011). This training could assist in avoiding problems that may arise during research projects such as budget over-runs, missed deadlines and problems with stakeholders (Payne *et al.*, 2011).

There is also little published information describing the use of project management health and medical research projects (Payne *et al.*, 2011; Aghayan *et al.*, 2014). There is also a skills transfer flaw in that project management processes are not transferred from project to project (Bongiovanni *et al.*, 2015). Lessons learned are not passed on and therefore most trials have to design management processes from scratch (Farrell, 1998). A more business-like approach has to be taken for the management of clinical trial projects whereby effective management systems and techniques are established and implemented (Farrell *et al.*, 2010; Goodarzynejad and

Babamahmoodi, 2015). Most of the literature on how to conduct or manage clinical trials is focused on the implementation and the day to day of all the moving parts that go into a clinical trial. Hagino (1991) offered guidance on how to write protocols, manage the budget and other administrative aspects of clinical trial. Farrell *et al.* (2010) attempted to offer a standardized managing clinical trials approach and even then, the focus was more on the efficient running of the moving pieces such as planning, recruitment, communications, collaborations and reporting.

2.4.4 Recommendations to resolve the management issues

2.4.4.1 Acquiring project management skills

Medical and healthcare professionals need to learn project management skills, and adopt them for the field of health and medicine (Aghayan *et al.*, 2014; Goodarzynejad and Babamahmoodi, 2015). Payne *et al.* (2011) recommended the use of project management as it has been shown to increase the effectiveness of health and medical research projects as well as communication and teamwork within those projects. A trained clinical project manager would apply project management principles to clinical research to ensure that all stages of a clinical trial are properly managed, that the objectives of the trial are achieved on time, on budget, and according to the GCP, and that the safety of the subjects participating in the clinical trial and the quality of collected data are guaranteed (Goodarzynejad and Babamahmoodi, 2015).

2.4.4.2 Portfolio Management Approach

For one intervention to be licensed, it has to be tested at all the different clinical trial phases and an arguably one phase can be considered to be a separate project. The objectives and outputs of a Phase I trial are different to that of a Phase III trial but collectively the end goal is the same. Bossert *et al.* (2002) recommended the use of systems approach for trials with multisite research where a system is more than the sum of its parts and that it functions as a whole. This would mean each phase would still have to be managed as a singular project using project management principles but collectively, the phases should be managed under one programme or even as a portfolio. Portfolio management is the centralized management of one or more portfolios, which

includes identifying, prioritizing, authorizing, managing, and controlling projects, programs, and other related works, to achieve specific strategic objectives (Aghayan *et al.*, 2014).

In healthcare system including health research many projects fail because of poor portfolio management (Aghayan *et al.*, 2014). Aghayan *et al.* (2014) recommends that clinical trials should have a Project Management Office (PMO) to increase the capability of clinical trials. PMO optimizes resource allocation and processes such as standardization, monitoring, auditing and data management (Aghayan *et al.*, 2014). PMO can help researchers to increase the efficiency of clinical studies by centralizing and consolidating of projects (Aghayan *et al.*, 2014). The use of portfolio management within a PMO ensures the best performance of its programs and projects by efficiently using resources and obtaining favourable outcomes that are impactful on health and medicine (Aghayan *et al.*, 2014).

All the above-mentioned project management principles will increase the chances that the clinical trials deliver their intended outcomes. The research will finish on time, within budget and with all the phases efficiently managed. The question then becomes, have the outcomes of the efficiently managed clinical research project brought about the desired purpose?

2.5 Benefits management

A well-managed research project could turn out to not have added the intended value to the intended stakeholders. A successful clinical trial has to run according to all the clinical trial guidelines and requirements but most importantly, the outcomes of clinical trials need to be clinically meaningful (Chew, 2011). How then do the investigators and managers ensure that the clinical trial fulfils its intended clinical purpose?

2.5.1 What are benefits?

At the beginning of every project or programme, a project owner's vision of a new desired state has to be clearly documented in the business case (Mossalam and Arafa, 2016). Projects are then

designed and used as tools to move from one state to the desired state hence closing the gap as shown in figure 9 (Serra and Kunc, 2015). At the end of each project life cycle, there are outcomes that result as part of the intended objectives of the project. It is these outcomes that bring about desired changes that result in positive strategic improvements known as benefits (Peppard *et al.*, 2007; Serra and Kunc, 2015).

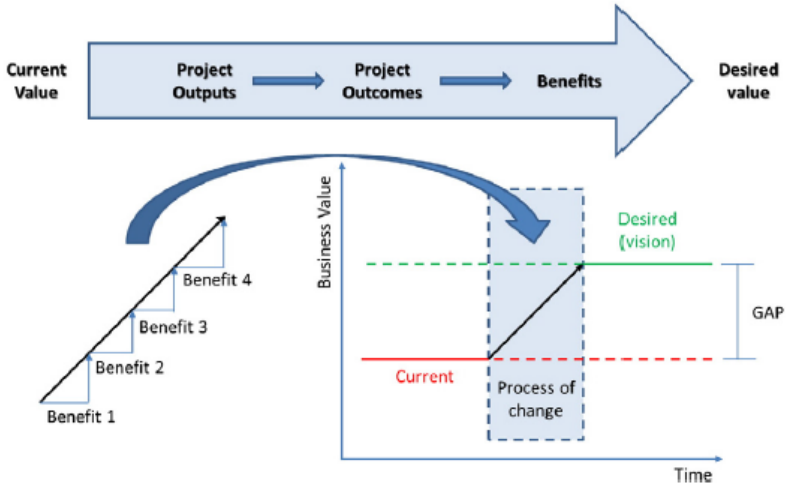

Figure 9 Benefits close the value gap. From (Serra and Kunc, 2015).

Benefits are measurable improvements resulting from outcomes (Sapountzis, 2013). Figure 10 shows the connections between outputs, change, benefits and strategic objectives. Project outputs bring about changes and these changes lead to benefits realization (Sapountzis, 2013).

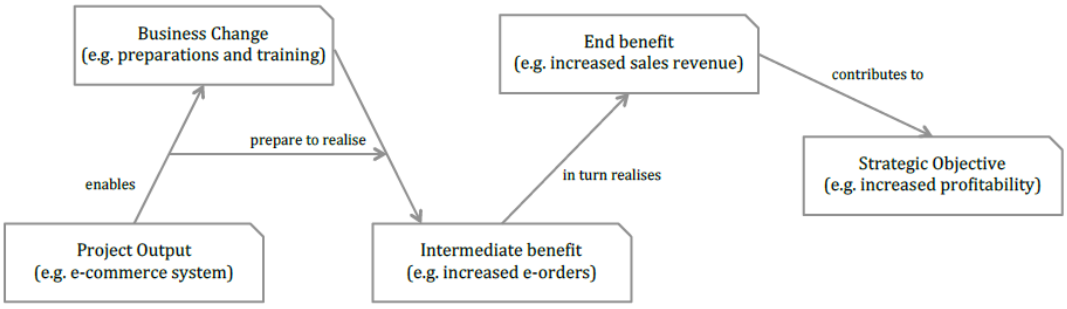

Figure 10 The relationship between project outputs, changes, benefits and strategic objectives (Sapountzis, 2013).

For projects and programmes to be regarded as successful, it is important that benefits are measured and confirmed (Sapountzis, 2013). The first step is for the organization is to move

away from an output focused style of management to a benefit orientated style of management (Chih and Zwikael, 2015). Output focused management is focused on managing inputs and outputs with the project objectives set on meeting agreed efficiency targets and the performance evaluation is on the iron triangle (time, budget and quality) (Chih and Zwikael, 2015). Benefit-oriented project management involves managing inputs and outputs with a focus on the ultimate realization of project benefits (Chih and Zwikael, 2015). When evaluating performance, it is important to make the distinction between project success and project management success (Chih and Zwikael, 2015). Project success is measured using time, cost or quality (Chih and Zwikael, 2015). Project success on the other hand, is measured by benefit realization (Chih and Zwikael, 2015).

"A successfully managed project is not the same as successful project (Mossalam and Arafa, 2016)".

2.5.2 Benefits realization management

In IT projects, Benefits Realization Management (BRM) is defined as the process of organizing and managing such that potential benefits arising from the use of IT, are actually realized (Ward *et al.*, 1996). BRM aims to bridge link between defined strategic benefits and project/programme management (Kagioglou and Tzortzopoulos, 2016). BRM is a process for the optimization or maximization of benefits from organizational change programmes (Sapountzis, 2013). BRM and its methodologies ensures that project and programs deliver what they promised (Lin and Pervan, 2003; Esteves and Dwivedi, 2009; Badewi, 2016). BRM can also be used to obtain benefits that are being lost and for identification of further benefits that could be discovered as the project is running (Lin and Pervan, 2003). Poor benefit management or the complete lack of it can be the cause of programme failure (Sapountzis, 2013).

There are numerous BRM frameworks in the literature that are proposed for realizing and assessing benefits (Divendal, 2011; Love *et al.*, 2014; Breese *et al.*, 2015). Some of these are:

- Active Benefits Management (ABM)(Leyton, 1995).
- The Cranfield process model of Benefits Management (Ward *et al.*, 1996).

- Benefits Management Approach (BRA) (Thorp, 1999)
- Process of Active Benefits Realization (Remenyi and Sherwood-Smith, 1998)
- The ABR Approach (Lin and Pervan, 2003)
- Towards Best Practice in Benefits Management (Ashurst and Doherty, 2003).
- Benefits Realization Management in managing successful Programmes (Bradley, 2006)
- Benefits Realization Capability Model (Ashurst *et al.*, 2008)
- Benefits Management in the handbook of Programme Management (Reiss *et al.*, 2006)

The Cranfield process model, shown in figure 2, appears to be the most applied BRM framework for delivering benefits and it is the preferred model for this work (Ward *et al.*, 1996; Lin and Pervan, 2003). These are the stages as they appear on the Cranfield model in figure 2.

2.5.2.1 Identifying benefits

Successful programmes tend to have well defined benefits that are without any vagueness (Sapountzis, 2013). Project benefits have to be well detailed and tied to outcomes that are aligned with the strategic goals (Ward *et al.*, 1996; Serra and Kunc, 2015). According to Chih and Zwikael (2015), there are seven criteria to consider when formulating target benefits and these are:

1. *Strategic fit:* the benefits have to align with the organization's overall strategy.
2. *Target value*: Each benefit has to have a baseline that will be used as a starting point when evaluating the benefit.
3. *Measurability:* The benefits must be measurable through the use of either a direct measure or an indirect indicator.
4. *Realism:* The benefits must be realistic, given the context in which the organization is operating and its constraints.
5. *Target date:* There has to be a set date for each benefit to be realized.
6. *Accountability:* for tracking purposes, each benefit must have an owner.
7. *Comprehensiveness:* the effects of each benefit must be analyzed from variety of aspects, be it operational, tactical and strategic level (Chih and Zwikael, 2015).

Benefits can be classified into tangible and intangible (Murphy and Simon, 2002). Tangible benefits are those improvements that can be measured by an objective and quantitative measure (Murphy and Simon, 2002). Intangible benefits however, are difficult to quantify and can only be judged subjectively and employ qualitative measures (Farbey *et al.*, 1999; Murphy and Simon, 2002; Love *et al.*, 2005; Ward and Daniel, 2006; Sapountzis, 2013). A tangible benefit for a clinical intervention would be years of healthy living added on and an intangible benefit would be the patient's confidence that the intervention will work. In IT project benefits can further be classified into several categories depending on the division the benefits impact. These categories and examples of each are shown in table 2.

Table 2 showing different categories benefits (Mirani and Lederer, 1998; Irani and Love, 2002)

Categories	**Examples**
1.Operational	1.1 Cost reduction, 1.2 Cycle time reduction, 1.3 Productivity improvement, 1.4 Quality improvement,
2. Managerial	2.1 Better resource management, 2.2 Improved decision making and planning 2.3 Performance improvement
3. Strategic	3.1 Support growth 3.2 Construct innovations 3.3 Generate product differentiation 3.4 Build external linkages
4. IT Infrastructure	4.1 build business flexibility for current and future changes 4.2 Increased data management capability
5. Organizational	5.1 Support organizational changes 5.2 Facilitate organizational learning 5.3 Empowerment 5.4 Built common visions

2.5.2.2 Benefits planning

Once the benefits are identified and described, a benefit realization approach requires careful planning and management (Ward *et al.*, 1996). Benefits should be planned at the beginning of the project and not at the end with the path from investment to benefit delivery effectively outlined (Sapountzis, 2013; Mossalam and Arafa, 2016). The changes that will lead to the desired outcomes have to be described, documented and communicated to all the relevant stakeholders (Ward *et al.*, 1996; Lin and Pervan, 2003; Serra and Kunc, 2015). The BRM plan has to be integrated with other branches of management for a holistic approach (Ward *et al.*, 1996; Lin and Pervan, 2003; Ashurst *et al.*, 2008; Serra and Kunc, 2015).

2.5.2.3 Benefits delivery

Benefits are not automatic and therefore it takes a well-designed benefits realization plan and great execution of that plan for their realization (Ward *et al.*, 1996; Ashurst *et al.*, 2008). A joint effort from the programme director, the project manager, the change manager and the benefits manager will bring about the changes that will deliver the benefits plan (Mossalam and Arafa, 2016). There are also unplanned benefits that may emerge as a result of the implemented changes or as a result of achieving primary benefits (Casarett *et al.*, 2002; Ashurst and Doherty, 2003; Sapountzis, 2013).

2.5.2.4 Benefits Review

During the life of a programme, the ability to deliver benefits may be affected by changes and unanticipated circumstances. These changes can come from within the programmes themselves or from environmental changes that affect the value of the benefits (Sapountzis, 2013). Benefits are measured in a systematic manner to show that added value (Ashurst *et al.*, 2008). Benefits can often be considered during the early stages of projects and tend to be forgotten and are not actively managed during the later stages (Ashurst *et al.*, 2008).It is therefore important that planned benefits have to be monitored so that they are not lost as the project continues (Sapountzis, 2013). New or intermediate benefits may also arise over the course of the project an event known as benefits creep (Sapountzis, 2013).

2.5.2.5 Benefits exploration

The practices required to realize the potential benefits from available information have to be adopted into the organizations way of doing things moving forward (Ward *et al.*, 1996). This requires organizational learning through monitoring and evaluation of benefits (Ward *et al.*, 1996; Ashurst *et al.*, 2008). This could in turn lead to finding additional benefits from the current and related projects (Ashurst *et al.*, 2008).

2.5.3 Role of BRM in general management

BRM is linked and connected to other management disciplines as shown in figure 11 (Breese, 2012). BRM has become very central to project, programme and portfolio management (Breese, 2012). Every project has to have a strategy on what has to be achieved and this has to be aligned with the available capability. Effectively bringing about the right changes leads to the intended benefits being realized.

Governance and Strategy: To realize benefits, changes have to happen from the top through effective governance. To "govern" is to have a controlling influence on, to have a direct effect on, or to fix or decide (Bekker and Steyn, 2008). Project governance is a set of management systems, rules, protocols, relationships and structures that provide the framework within which decisions are made for project development and implementation to achieve the intended business or strategic motivation (Bekker and Steyn, 2008).

The most important link of BRM to general management of projects is that the benefits must be aligned with the strategy (Sapountzis, 2013; Mossalam and Arafa, 2016). It is important to start any project or programme with the end in mind, this way, the changes and the resulting outcomes are related to strategic objectives (Sapountzis, 2013; Mossalam and Arafa, 2016). Effective project governance is an important catalyst for the development and leadership of a benefit management process in projects (ul Musawir *et al.*, 2017). Although the interaction between project governance and benefit management process is more complex than a simple cause-and-effect relationship, project governance creates the roles, responsibilities, and

accountabilities that enable benefit management (ul Musawir *et al.*, 2017). Project governance is effective in improving project success and supporting organizational strategy if key governance roles adopt a benefits-oriented approach (ul Musawir *et al.*, 2017). Reasoning for initiating a project and justification for the required investments is usually stated in business case which is a tool that supports planning and decision making (Divendal, 2011). A business case can ensure commitment from managers by describing the changes that will deliver the identified benefits and demonstrating a basis for the actually delivery of those benefits (Divendal, 2011).

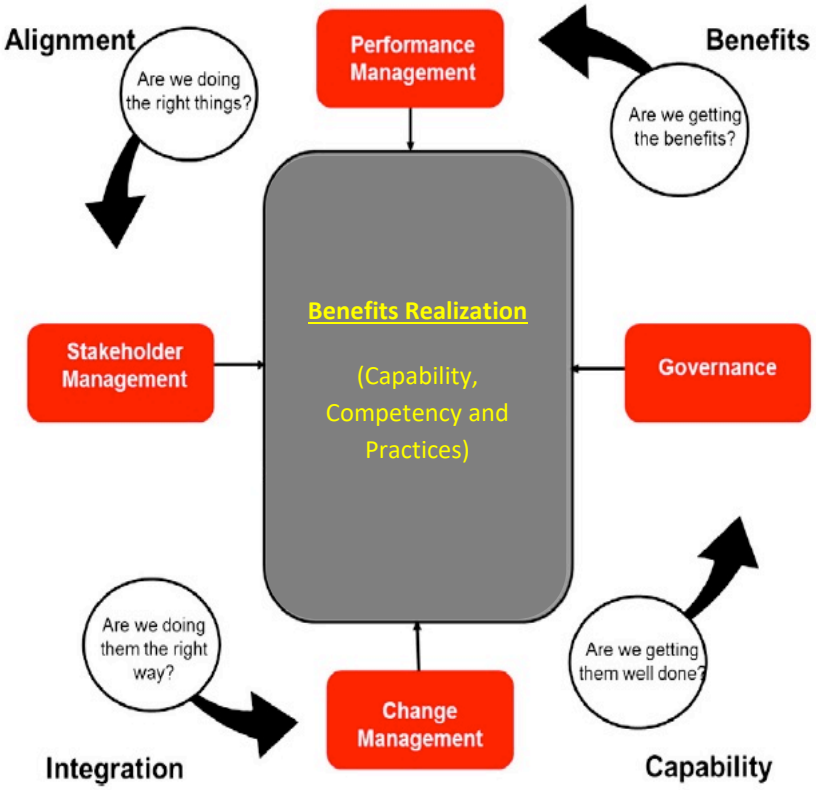

Figure 11 Interaction between several management disciplines and BRM (Love *et al.*, 2014).

Change management: Change management is essential and central to BRM as benefits do not simply occur through the insertion of changes within organizational processes (Sapountzis, 2013). Benefits arise when the people in the organizations embrace the changes in their business processes (Sapountzis, 2013). Previous studies highlight the importance of essential organizational changes that lead to successful benefits realization from system development

projects (Doherty *et al.*, 2012). Some of these changes include utilizing successful delivery methods such as programme management (Mossalam and Arafa, 2016).

Programme management: Programmes themselves rarely deliver benefits directly, but by combining projects and their deliverables to create the capabilities that enable the desired benefits to be achieved (Sapountzis, 2013). The benefits of each project can only be derived when combined with outcome of other projects (Sapountzis, 2013).

Performance management: By developing a benefits culture, BRM creates a system where continuous evaluation ensures that the processes deliver benefits (Sapountzis, 2013; Mossalam and Arafa, 2016). This culture influences both performance management and stakeholder management as the well-defined benefits have to be communicated to stakeholders at the outset to ensure that the stakeholders are committed to benefits (Sapountzis, 2013; Mossalam and Arafa, 2016).

Mossalam and Arafa (2016) proposed that moving forward BRM processes should be merged into most of project, programme or portfolio management processes. It is important to be mindful of the planned benefits throughout the lifecycle of a project that is straight from initiation and past the closeout. It is also important to cater for benefits management once the project has been closed out to allow for benefits transition and sustainability.

2.6 Benefits management in clinical trials

Benefits management in clinical trials is driven by There is a principle in clinical research known as beneficence. Beneficence campaigns for maximizing possible benefits and minimizing possible harms as demonstrated in figure 12 (Emanuel, 2000; Rid *et al.*, 2010; Grankvist and Kimmelman, 2016; Koonrungsesomboon *et al.*, 2016; Resnik, 2017).

Figure 12 Risk-benefit assessment and justification.

2.6.1 Risk-benefit assessment of a clinical trial

IRB determine whether the balance between the risks and benefits of a proposed study is reasonable or proportional (Musschenga *et al.*, 2007). Useful clinical research has to address a health problem, build on existing knowledge and prioritize the patient (Ioannidis, 2016). The clinical trial must show value for money while being transparent (Ioannidis, 2016). IRB compare risks and benefits, but do not weigh them against each other as IRB generally lack conceptual frameworks for identifying and assessing risks and benefits (Musschenga *et al.*, 2007). Benefit assessment in clinical research is not well conceptualized and is often ad hoc, rather than standardized and systematic (Churchill *et al.*, 2003; Barke, 2009).

There are limitations and challenges in describing scientific benefits with greater specificity can and the lack of specificity can have adverse consequences (Emanuel, 2000; King, 2000; Churchill *et al.*, 2003). The vagueness in the description of benefits contributes to therapeutic misconception in subjects and leads to overestimation of the likelihood of benefits (Churchill *et al.*, 2003). Candilis *et al.* (2006) has questioned the overall decision-making process of the IRB as the lack of a set criteria is a clear limitation. As a guide for IRB decision making, the Belmont Report and Common Rule only requires that participants should be provided with a description of any benefits that may be "reasonably" expected from the research (Musschenga *et al.*, 2007). Even if the risks are minimal, some clinical research might have non-generalizable results that are

unlikely to be disseminated or in which the intervention could never be practically implemented even if effective (Barke, 2009). This means that risk-benefit decisions are made without a clear criteria and in the face of uncertainty with regard to patient benefits and study rationale (Musschenga *et al.*, 2007; Van Luijn *et al.*, 2007).

2.6.2 Uncertainty

Aside from the beneficence obligation, clinical research is also surrounded by uncertainty. Early phase trials represent the point of maximum uncertainty about both the safety and utility of new interventions (Barke, 2009; Grankvist and Kimmelman, 2016; Habets *et al.*, 2017). Only 8–10% of the interventions entering early stage studies lead to market authorization and less than 8% of these approved drugs offer an increased therapeutic benefit over existing drugs (Light *et al.*, 2013; Hay *et al.*, 2014; Habets *et al.*, 2017).

2.6.3 Quality Assurance

There are also quality concerns about the high throughput of publications of findings from clinical trials (Borgerson, 2016). A study that analysed 400 clinical studies in the United States revealed that 30% had not shared results through publication or through results reporting in ClinicalTrials.gov within 4 years of completion (Saito and Gill, 2014). There is also evidence of a lack of consistency in following trial protocols and selective reporting by researchers (Al-Marzouki *et al.*, 2008). Researchers elect only to reveal favourable outcome of trials which brings up a question of reliability in the reports (Al-Marzouki *et al.*, 2008). With the high quantity and low quality, practitioners battle to consume it all and most of it ends up being of no benefit to the patients (Borgerson, 2016).

2.7 This Study

The benefits of scientific research are complex and difficult to predict (Barke, 2009). It is because of this complexity and the uncertainty with clinical trials as well as the need to ensure clinical

utility, that Ioannidis (2016) argued that reform and improvement to performing clinical research are overdue. Continuous improvement approach is a philosophy of on-going improvement which involves everyone in the organization on a day to day basis in a constant quest for continuous incremental improvement on all fronts (Thorp, 1999; Sapountzis, 2013). The philosophy simply starts with documented processes for simplicity and improvement. Once the improvements have been made, the improvements are standardized and integrated into the organization's processes. Moving forward, the performance of the new processes are monitored and the whole processes repeated (Jha *et al.*, 1996; Sapountzis, 2013). There is an element of "Plan-Do-Check-Act" cycle for continuous improvement (Sapountzis, 2013).

The willingness to constantly improve and better the organizational approach and processes and using lessons learnt from project to project, would be a way to address achieving the intended purpose of clinical projects (Thorp, 1999; Sapountzis, 2013). There seems to be a need and room for application of BRM processes in clinical research to ensure that all the benefits are realized and maximum value is derived. There is evidence that the use of BM practices enhances the likelihood of projects achieving organisational goals (Ward and Daniel, 2006; Serra and Kunc, 2015). With proper application of management principles and BRM, a clinical trial should be completed on time and on budget and should serve its intended purpose. Guidelines on how to manage clinical trials are useful and key to the success of clinical trials, however, there is a gap and room for continuous improvement on how to manage and evaluate the intended purpose of the clinical trial (benefits).

This work is intended to add to the existing clinical trials management knowledge by proposing the idea of incorporating existing guidelines/processes used currently to manage clinical trials and BRM processes that have been used to manage benefits of projects in other industries. This is with the assumption that there is a need for these processes and that there is a benefits management limitation in the existing processes. Benefits management needs to be integrated into existing project management practices rather than simply "bolted on" (Ward *et al.*, 1996; Sapountzis, 2013). An integrated management model that merged existing project management

and benefits management processes has been shown to work (Mihić *et al.*, 2012; Mossalam and Arafa, 2016). In Serbia, the projects management processes of energy efficiency in public buildings was integrated with those of benefits management and this improved the achievement of maximum benefits for the community (Mihić *et al.*, 2012). The intergraded model achieved benefits such as energy savings, greenhouse gas reduction, comfort improvement, etc. (Mihić *et al.*, 2012).

3 Research Methodology

3.1 Research Purpose

There is an ongoing need for effective diseases interventions. The path to obtaining an intervention that has been certified safe and effective, is that of uncertainty and risks to the human participants of clinical trials. This work aimed to explore the management practices and processes that are used to increase the chances of the intended benefits of a clinical trial, being realized. This was done using a systematic inquiry of the defined research problem using appropriate methods to gather adequate and representative evidence (Amaratunga *et al.*, 2002).

3.2 Research Philosophy

Understanding the assumptions about knowledge and reality that underpin research was useful in designing and interpreting this research (Bunniss and Kelly, 2010). There are several distinct philosophical approaches to developing research (Amaratunga and Baldry, 2001). Paradigms are sets of beliefs and practices, shared by communities of researchers, which regulate inquiry within disciplines (Bunniss and Kelly, 2010). The various paradigms are characterised by differences in their ontological (nature of reality), epistemological (nature of knowledge) and methodological (nature of approach to research) approaches to conceptualising and conducting research (Bunniss and Kelly, 2010). There are several major paradigms positivism, post-positivism, interpretivism and critical theory shown greater detail in table 7 in Appendix A (Bunniss and Kelly, 2010). For this study, positivism and interpretivism were considered as they are two commonly used epistemological stances to know about the world (Ritchie *et al.*, 2013).

3.2.1 Positivism

Positivism searches for causal explanations and fundamental laws, and generally reduces the whole into its simplest possible elements in order to facilitate analysis (Amaratunga and Baldry, 2001). The positivism approach focuses on facts and considers the world to be independent of and unaffected by the researcher (Amaratunga and Baldry, 2001; Bunniss and Kelly, 2010; Ritchie

et al., 2013). There is a need to formulate hypotheses and test them (Amaratunga and Baldry, 2001). Positivism relies on numbers and the skills of the researcher as a mathematical or statistical analyst (Ritchie *et al.*, 2013). The subject under analysis should be measured through objective methods rather than being inferred subjectively and through sensation, reflection or intuition (Amaratunga and Baldry, 2001).

3.2.2 Interpretivism

The basic belief is that the researcher and the social world impact on each other (Ritchie *et al.*, 2013). Facts and values are not distinct which means findings are inevitably influenced by the researcher's perspective and values, thus making it impossible to conduct objective, value free research, although the researcher can declare and be transparent about his or her assumptions (Amaratunga and Baldry, 2001; Bunniss and Kelly, 2010; Ritchie *et al.*, 2013). The interpretative approach understands reality as holistic and socially constructed rather than objectively determined (Amaratunga and Baldry, 2001). The interpretative approach tries to understand meanings and explain a phenomenon, rather than search for external cause or fundamental laws (Amaratunga and Baldry, 2001). Ideas are developed through induction from data (Amaratunga and Baldry, 2001; Bunniss and Kelly, 2010).

3.3 Research Approach

The interpretivism approach was adopted for this study to evaluate the current use and application of BRM processes in clinical trials. The positivism approach was not applicable in exploring the existence on BRM processes in clinical trials as the exploration was based on subjective views and opinions of management. The positivism approach involves making predictions or using scientific experiments to describe or measure a phenomenon and this was not a possibility for this study. It was therefore decided that to accurately address the research goals of this study and to achieve enough depth, an interpretivist methodology approach was adopted.

3.3.1 Quantitative or qualitative data

The research approach used would yield qualitative findings due to the inductive nature of the study to describe BRM processes and evaluate the effectiveness of those processes. Qualitative research, broadly defined, means any kind of research that produces findings not arrived at by means of statistical procedures or other means of quantification (Golafshani, 2003). Qualitative research is best characterized as a family of approaches whose goal is understanding the lived experience of persons who share time, space and culture (Frankel and Devers, 2000a). The logic of qualitative research is often inductive, rather than deductive, and consists of describing people's and groups' particular situations, meanings and experiences (Frankel and Devers, 2000b).

In contrast, quantitative research employs deductive logic, often drawing heavily on existing theoretical and substantive prior knowledge to conceptualize specific situations, and to predict what will happen to particular people or groups, and why (Frankel and Devers, 2000b). Quantitative research could not be used in this study as it would require experimental methods, testing of hypothetical generalizations using some unit of measurement and analysing causal relationships between variables (Golafshani, 2003). Quantitative research emphasises facts and causes of behaviour and the information is in the form of numbers that can be quantified and summarized (Golafshani, 2003). The mathematical process is the norm for analysing the numeric data and the final result is expressed in statistical terminologies (Golafshani, 2003).

The qualitative research process is emergent, non-linear and non-sequential as data collection and analysis often proceed simultaneously (Frankel and Devers, 2000b). In light of early findings, subsequent data collection and analysis procedures may be modified to gather more specific information, or explore new and unanticipated areas of interest (Frankel and Devers, 2000b). The researcher and research subjects, their relationship, and the research setting are all subject to development and change (Frankel and Devers, 2000b). Commonly used qualitative research tools include the field work approach, interviews and surveys, audio-visual records, and the study of documents (Frankel and Devers, 2000a). Qualitative research approaches are only as good as

the questions they set out to illuminate (Frankel and Devers, 2000a). Good qualitative studies answer clearly stated, important research questions and how these questions are formulated has implications for conducting the research (Frankel and Devers, 2000b).

3.4 Sampling Strategy

Sampling is used because studying whole populations can be expensive and/or not feasible (Bhattacherjee, 2012). Sampling is therefore used to study a subset of a population of interest for purposes of making observations and statistical inferences about that population (Bhattacherjee, 2012). This study used purposive sampling strategy rather than random sampling strategies. Purposive sampling strategies are designed to enhance understandings of selected individuals or experiences of groups by selecting "information rich" cases, that is individuals, groups, organizations, or behaviours that provide the greatest insight into the research question (Devers and Frankel, 2000). Another advantage of purposive strategies is that the strategy can be revised throughout the research process as more knowledge of the setting and subjects are obtained (Devers and Frankel, 2000).

HIV clinical trials were used to explore a multi-perspectival understanding of the application of BRM processes in clinical trials and evaluate the perception of their efficiency. It is important to include cases in a study that offer an opportunity for learning (Tellis, 1997; Bhattacherjee, 2012). This lead to the choice of multiple clinical trials under one area, HIV research, to strengthen the results by replicating the pattern matching, thus increasing confidence in the robustness of the theory (Amaratunga and Baldry, 2001). This strategy was intended to set the investigation of BRM processes operating in a real-life context and to collect multiple perspectives from people with different viewpoints on what is being observed to build up detailed and in-depth understanding.

A pilot questionnaire was used for the first few accessible participants to check and/or verify the quality of the questions. The questionnaire was then adjusted accordingly for subsequent correspondents to improve the comprehensiveness of the data collection. There was flexibility incorporated into the approach specifically when choosing people to contact and include in the

study. This was shaped by the ongoing findings, the ease of access to individuals and recommendations from those that had already participated in the study. This approach was similar to case study research in that it included some deduction based on prior theory as shown in figure 13 (Perry, 1998). Prior theory and theory emerging from the data are always part of any study as and that it is impossible to go theory-free into any study (Perry, 1998).

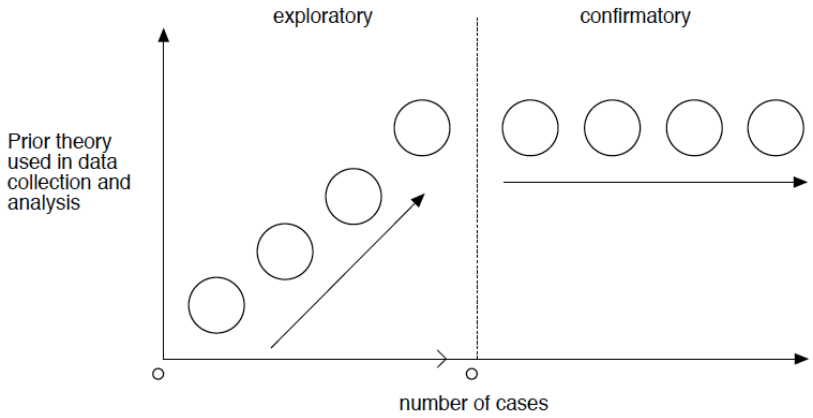

Figure 13 Inductive and deductive approaches to case study research (Source: Perry (1998))

The first case on the left hand side of the figure is almost pure grounded theory (Perry, 1998). But data collection and analysis of the next cases on the left-hand side is informed by preliminary concepts from the first case and from prior theory (Perry, 1998). This prior theory then informs the interview protocol used for data collection in all the main cases, as shown on the right-hand side (Perry, 1998).

It is important to highlight that the probability of the selection in this study cannot be accurately determined as the sample selection was based on a non-random criteria of expert sampling of clinical trials management and convenience (Bhattacherjee, 2012). The sampling frame used may therefore not be entirely representative of the population at large and inferences from this study may not be generalizable (Bhattacherjee, 2012).

3.5 Research Instrument

The study was in two parts with the first part being a critical review of documented BRM processes in several general clinical trial guidelines referenced by HIV publications. The second part of the study considered different perspectives of the actors involved in management of clinical trials. The advantages and disadvantages of each method is shown in table 3.

Table 3 The use of studying of documents and the online survey (adapted from (Frankel and Devers, 2000a)

	Typical focus	**Advantages**	**Disadvantages**
Study of documents	Process outcomes	• Relatively easy to obtain • Maybe compared against selected criteria • Unobtrusive	• Can be bulky, difficult to transport and code • Issues of accuracy and completeness difficult to assess • Social context of document production difficult to reconstruct
Surveys	Attitudes and beliefs	• Can be administered to a large number of subjects • Relatively inexpensive way of sampling opinions, attitudes and values • Results are easily quantified • Generalizable	• Limited or fixed choice questions may give results that are not factual • Little control over context of responses • Difficult to assess overall accuracy of responses • Potential for oversimplifying issues

3.5.1 Part 1: Critical review of clinical trials guidelines

This section of the study will take format of a literature review of the guidelines documents that were used in HIV clinical trials. The documents will be systematic searched for any mention of BRM processes and/or proposed approaches to maximizing clinical research benefits. The

following protocols and ethical guidelines as well as other publication linked with HIV clinical trials were reviewed for the mention of BRM processes and/or context:

- The Nuremberg Code, 1947
- Declaration of Helsinki, 1964 (last updated in October 2000)
- The Belmont Report, 1979
- The CIOMS Guidelines, 1982 (last updated in 2002)
- Ethical Considerations in HIV Preventive Vaccine Research: UNAIDS Guidance Document, 2000
- Good Participatory Practice: Guidelines for Biomedical HIV Prevention Trials, revised: UNAIDS Guidance Document, 2011

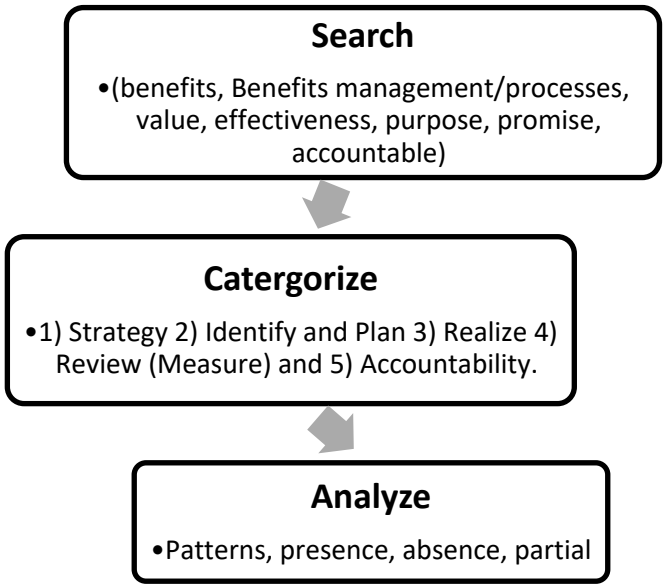

Figure 14 Reviewing Guidelines.

The keywords search included: *benefits, benefits management, benefits processes, benefits assessment, value, effectiveness and purpose.* The results were categorized into areas of BRM focus such as strategy, benefit identification and benefit planning, benefit realization, benefit review and benefit measure. The relevant matches that resulted from the searches were grouped, analysed and tabulated.

3.5.2 Part 2: Survey

The second section of the study was an exploratory cross-sectional assessment of currently applied BRM processes as perceived by people actively involved in the management of past or ongoing HIV clinical trials. Survey research method involves the use of standardized questionnaires to collect data about people and their preferences, thoughts, and behaviours in a systematic manner (Bhattacherjee, 2012).

The survey research was used because its inherent strengths compared to other research methods. As stated by Bhattacherjee (2012), these include:

1. Excellent for measuring a wide variety of unobservable data, such as people's preferences, traits, attitudes, beliefs, behaviours or factual information.
2. Remotely collecting data about a population that is too large to observe directly.
3. Questionnaire surveys are preferred by some respondents due to their unobtrusive nature and the ability to respond at one's convenience.
4. Survey research is economical in terms of researcher time, effort and cost than most other methods such as experimental research and case research.

The questions used in survey research may be unstructured or structured (Amaratunga and Baldry, 2001). The unstructured questions ask respondents to provide a response in their own words, while structured questions ask respondents to select an answer from a given set of choices (Amaratunga and Baldry, 2001). The responses of the subjects to individual questions on a structured questionnaire may be aggregated into a composite scale or index for statistical analysis. (Amaratunga and Baldry, 2001).

Questionnaires were used establish the knowledge of the managers of any BRM processes for ensuring benefits realization and whether those processes, if any, were being used in practice in HIV clinical trials. The first contact was with easily accessible participants within the field through emails with link to the online survey. This served as a pilot questionnaire to check and/or verify

the quality of the questions. The questionnaire was then adjusted accordingly for subsequent correspondents. The pre-set categorized questions were sent as they appear in appendix B.

3.6 Data Analysis Technique

This was a qualitative study and the collected data were recorded in coded manner that enables analysis with programs such as SPSS for Windows. The data portrayed the current practices of BRM in clinical trials and reveal how advanced they are. Data analysis consisted of examining, categorizing and/or tabulating the evidence to address the initial propositions of a study (Tellis, 1997; Bhattacherjee, 2012) .

3.7 Research Instrument validation

Reliability and validity demonstrate trustworthiness, rigor and quality of qualitative research (Golafshani, 2003). Triangulation is used to achieve validity and reliability of research affected by the perspectives of the researcher and to eliminate bias about some social phenomenon (Golafshani, 2003). Triangulation is a validity procedure where researchers search for convergence among multiple and different sources of information to form themes or categories in a study (Golafshani, 2003). It was for triangulation purposes that this study was in two parts with the first part being a critical review of documented BRM processes in several general clinical trial guidelines referenced by HIV research publications and the second part of the study considered different perspectives of the actors involved in management of clinical trials.

Surveys have been shown to generally have low response rates and this bring up reservations about their validity and bias (Radhakrishna and Doamekpor, 2008; Fan and Yan, 2010). To avoid most of the factors that lead to low response rates, specifics attempts to better the survey development as proposed by Fan and Yan (2010), were implemented. These attempts included running pilots surveys, having multiple draft versions to remove deterring elements such as length and making the subject interesting and relevant (Fan and Yan, 2010).

3.8 Develop the conclusions, recommendations and implications

Logical reasoning was employed in drawing conclusions on the basis of the evidence without any bias. Attempts to demonstrate the validity or reasonableness of the conclusions we also undertaken. Any existing processes were compared with theoretical and published BRM processes commonly applied in IS/IT projects to establish the degree to which BRM processes are present in clinical trial research. This study will enable the assessment of the as-is benefits management situation in clinical trials.

3.9 Potential limitation of the approach:

The main reason this approach was taken was due to a limitation in the amount of time available to fully explore this phenomenon. Retrieving documents can be difficult and extracting useful data from said documents can be subjective and open to interpretation. It is possible that access and usage of information from these may be blocked by gatekeepers in this field (Devers and Frankel, 2000). There is always that possibility that the questions could have been better phrased opening the process up to misinterpretation. There could also be response bias from the participants.

Survey research has disadvantages as it is subject to a large number of biases (Bhattacherjee, 2012). There is the non-response bias which occurs when a small group responds and is not fully representative (Bhattacherjee, 2012). There is sampling bias that results due to the method of the survey, whereby there is a chance a group of people that do not have access to a platform used and are left out (Bhattacherjee, 2012). Social desirability bias is a result of participants may offer altered responses to safe face. Other potential biases include the recall bias where the participants maybe responding to questions in which they do not remember most of the relevant details and the common bias which is when the phenomenon under investigation may not be adequately separated from measurement artefacts (Bhattacherjee, 2012).

Quality of a study in each paradigm should be judged by its own paradigm's terms (Golafshani, 2003). While the terms reliability and validity are essential criterion for quality in quantitative paradigms, in qualitative paradigms the terms credibility, neutrality or confirmability, consistency or dependability and applicability or transferability are to be the essential criteria for quality (Golafshani, 2003).

3.10 Research Ethics

Ethics is the moral distinction between right and wrong and what is unethical may not necessarily be illegal (Bhattacherjee, 2012). It is difficult to predict ethical predicaments that may arise from a research study but it is important to still to be aware of most of the ethical consideration and to take necessary steps to address them (Orb *et al.*, 2001; Bell and Wray-Bliss, 2009; Houghton *et al.*, 2010). Here are some of the ethical considerations that were considered throughout this study:

Disclosure: The participants were fully informed about the nature of the research through an explanatory covering email and/or an explanation before the questions (Orb *et al.*, 2001). The researcher, along with his supervisor's contact details will be provided and the participants can contact the researcher should they have any questions and or queries regarding study.

Non-maleficence: The people that were approached were made aware that they would not be harmed as a result of their participation or non-participation in the study (Bhattacherjee, 2012). The risk of participating in this research, never outweighed the importance of the problem being studied.

Voluntary participation: The participants were aware that their participation in the study was voluntarily and that they had the freedom to withdraw from the study at any time without any unfavourable consequences (Bhattacherjee, 2012). The participants were also made aware of the criteria used to select them as ideal candidates for the study.

Informed consent: All participants were issued and signed informed consent forms that clearly described their right to not participate and a right to withdraw before their responses in the study are reported (Houghton *et al.*, 2010).

Confidentiality: The identity of the participants was not divulged in the report to protect their interests and future well-being (Bhattacherjee, 2012). No personal or sensitive details of the participants were collected.

Analysis and reporting: All findings were reported without influence of the researcher and participant relationship or the researcher's subjective interpretations of data or the impact on the intended research (Orb *et al.*, 2001; Houghton *et al.*, 2010).

Conflicts of interest: There were no potential conflicts of interest to declare.

The research protocol was provided to the University of Cape Town Ethics Committee for review and approval, with study commencing once approval was granted. All data and information collection during this study was kept strictly confidential, with the researcher maintaining sole access to the data.

3.11 Research Methodology Summary

Table 4 Summary of the research methodology

Research Philosophy	Interpretive
Research Approach	Qualitative
Data Collection Method	Literature and policy Review Survey Questionnaires
Data Analysis Technique	Thematic analysis

4 Results

This chapter presents the findings from both parts of this study. The first part was the critical review of documented BRM processes in several general clinical trial guidelines referenced by HIV publications. The second part of the study considered different perspectives of the actors involved in management of clinical trials using the survey questions in appendix B.

4.1 The research tools

The official documents that were reviewed were either clinical trial protocols, standard operating procedures, policies, guidelines and publications that appear in table 6. All the respondents of the survey were at different levels of management for the different HIV clinical trials and had diverse professional backgrounds as shown in table 5.

Table 5 showing the occupations of the people that responded to the survey

Positions occupied by people who responded to the survey
Principal investigators
Programme lead
Director
Statistician
Protocol chair
Research officer
Project managers
Program manager
Protocol chair
Research coordinator
Nurse
Medical scientist

14 of the 19 respondents in this study claimed to have been involved at the planning phases of their respective clinical trials and shown in figure 15.

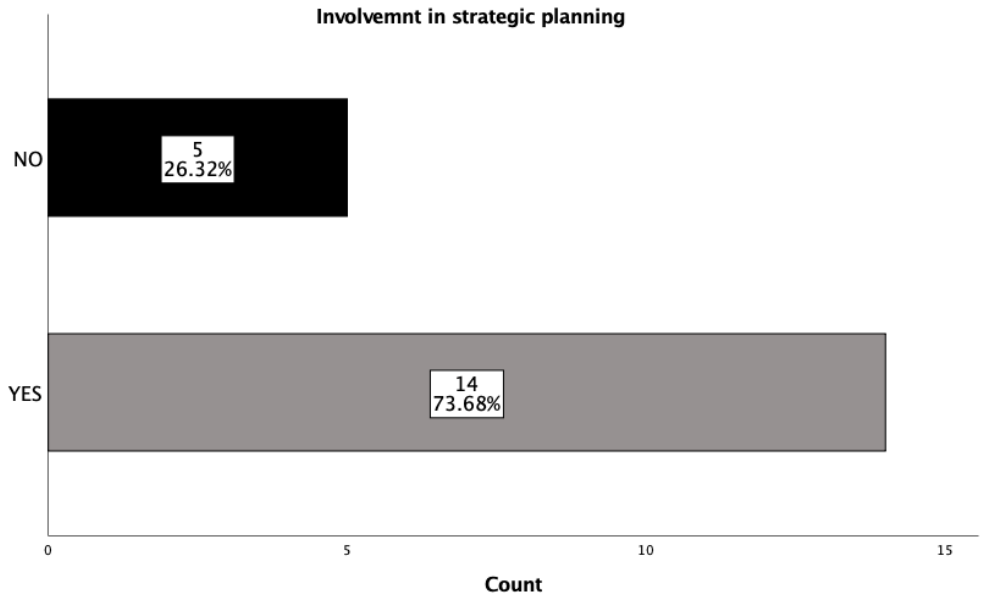

Figure 15 Inclusion of the respondent during planning

4.2 Are there comprehensive benefits management processes in HIV clinical trials?

4.2.1 Review of clinical trials documents and guidelines

In order to identify BRM processes used to manage HIV clinical trials benefits, keyword searches of publicly available HIV clinical trials documents were conducted. Aspects of benefits managements that were found in these documents are detailed in table 6 and were grouped into aspects that belong under benefits management plan, benefits identification, benefits planning, benefits measuring, benefits realization, benefits review, benefits review and benefits report.

In the multiple documents and guidelines that were reviewed, there were no clearly detailed, separate and documented benefits management processes in HIV clinical trials. There are however, processes that were arguably elements of BRM that are alternatively termed and incorporated within other managements processes but appear to be aimed at managing benefits. These are processes in the general management and approach to clinical trials that include aspects that bear similarity to processes in IT/IS benefits management.

Table 6 Different sections that are benefits related or relevant that have been extracted from multiple documents and guidelines used in HIV clinical trials

	WHO Handbook for good clinical research practice (GCP): guidance for implementation	**ICH Harmonised Tripartite Guideline: Guideline for good clinical practice**	**World Medical Association Declaration of Helsinki**	**Consolidated Standards of Reporting Trials CONSORT**	**Food and Drug Administration (FDA)**	**Pragmatic Explanatory Continuum Indicator Summary 2 (PRECIS-2) Tool**	**The Belmont Report**	**The Nuremberg Code**
Benefits management plan	Beneficence A favourable risk/benefit assessment;	X	X	X	The federal regulations do not define "direct benefits" nor explain how they differ from indirect benefits or other types of benefit (Ross, 2006).	X	The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research	X
Benefits Identification	Principle 3: Before research involving humans is initiated, foreseeable risks and discomforts and any anticipated benefit(s) for the individual research subject and society should be identified.	X	X	X	Risks to subjects are reasonable in relation to the anticipated benefits. *(CFR) 45 part 46:* it is necessary to determine whether the research offers the prospect of direct benefit as long the risk is justified by the anticipated benefit to the subjects (Ross, 2006).	X	X	Yield fruitful results

Table 6 (continued)

	WHO Handbook for good clinical research practice (GCP): guidance for implementation	ICH Harmonised Tripartite Guideline: Guideline for good clinical practice	World Medical Association Declaration of Helsinki	Consolidated Standards of Reporting Trials CONSORT	Food and Drug Administration (FDA)	Pragmatic Explanatory Continuum Indicator Summary 2 (PRECIS-2) Tool	The Belmont Report	The Nuremberg Code
Benefits Planning	Principle 4: Research involving humans should be initiated only if the anticipated benefit(s) for the individual research subject and society clearly outweigh the risks. Although the benefit of the results of the trial to science and society should be taken into account, the most important considerations are those related to the rights, safety, and well-being of the research subjects.	X	Institutional Review Boards (IRBs) should weigh the risks of medical research against its benefits, and to assess the ratio between them	X		X	X	X
Benefits measuring	A favourable risk/benefit assessment.		X	X	Only those within the research, Not outside or later	X	X	X
Benefits realization	X		X	X	X	X	X	X
Benefits Review	X		X	X	X	X	X	X
Benefits report	X		X	X	X	X	X	X

4.2.2 The online survey

4.2.2.1 The survey metrics

The survey response rate is defined as the number of completed units divided by the number of eligible units in the sample (Fan and Yan, 2010). In this study over 2000 emails with the link to the survey were sent out. The e-mail addresses were obtained from websites and directories of the several research groups and networks that work with HIV clinical trials. A copy and paste approach was used and this made it difficult to keep track of the exact number of emails sent out. This was further complicated by failed-to-sent email addresses that were either deactivated or rejected the survey e-mail as spam. The exact response rate number of this study is therefore unknown but with only 19 responses from the numerous emails that were sent out, the response rate was assumed to be low.

4.2.2.2 Familiarity with BRM and BRM processes

Only 1 individual out of the 19 respondents was aware of BRM and had actually applied BRM processes to manage clinical trials. When asked about their familiarity with BRM, 74% of the respondents stated that they had never heard of BRM and BRM processes as shown on figure 16. The remaining 20 percent admitted to not using BRM processes even though they were familiar with them.

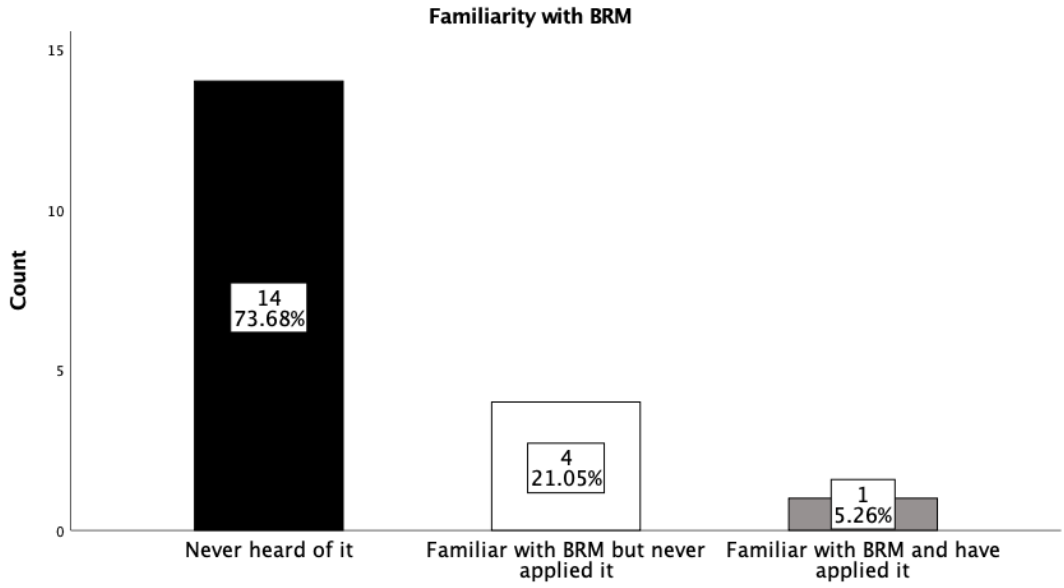

Figure 16 Showing the respondents' familiarity with BRM and BRM processes

When asked about the existence of comprehensive processes used to manage benefits of clinical trials, 74% of the respondents believed that BRM processes existed in HIV clinical trials even though they were not familiar with BRM processes as shown in figure 17. These were some of the comments from the participants when asked about the existence of BRM processes in HIV clinical trials:

"I am not aware of any but that doesn't mean they don't exist."

and

"I assume yes but not aware of any direct frameworks used."

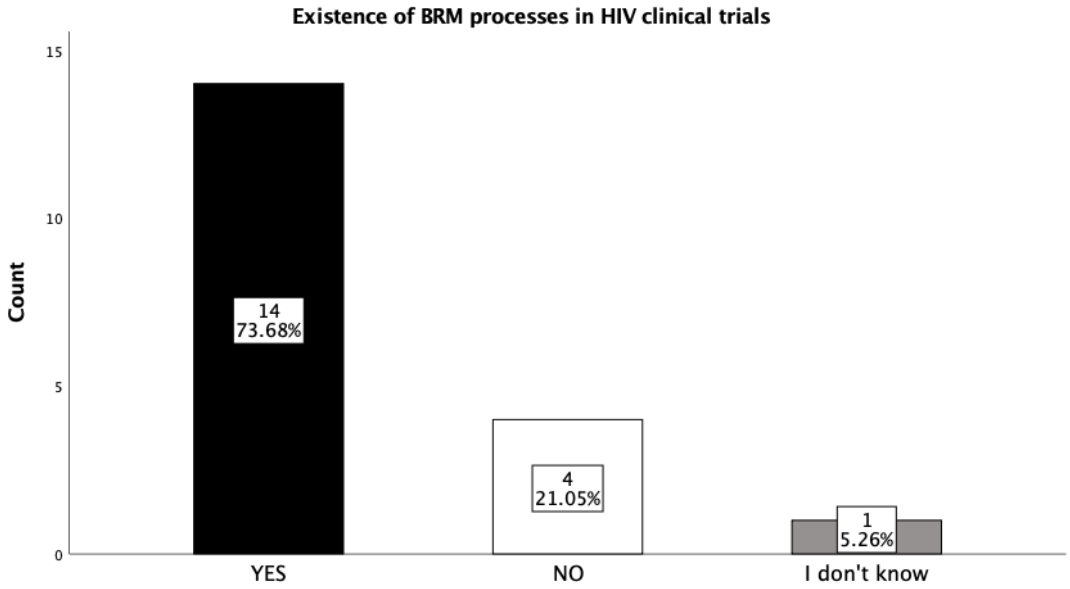

Figure 17 The respondents believed that BRM processes existed in HIV clinical trials.

4.3 What are the current benefit management practices in HIV clinical trials?

4.3.1 Review of clinical trials documents and guidelines

There are detailed guides on important processes to include in clinical trials management but there is limited information on benefits management processes. Most of the methods are more about standardising the day to day management approaches or output focused. There were however, processes specific to clinical trials that also appear be used for managing benefits in

clinical trials or show similarity to IT/IS BRM processes. The list below sums up what is listed on table 6 and what each document includes.

- *WHO Handbook for good clinical research practice (GCP): guidance for implementation*: There are aspects of this document that speak to benefits planning and identification.
- ICH Harmonized Tripartite Guideline: Guideline for good clinical practice: no aspects of benefits management were identified.
- World Medical Association Declaration of Helsinki: Only highlighted identifying more benefits than risks.
- Food and Drug Administration (FDA): There are aspects of the FDA documents that touch on benefits planning, identification and measuring.
- *Consolidated Standards of Reporting Trials CONSORT* and *Pragmatic Explanatory Continuum Indicator Summary 2 (PRECIS-2) Tool*: These two documents only mention how to report clinical trials but there was no mention of benefits in both of the documents.
- *The Belmont Report*: Touches on aspects of benefits assessment.
- *The Nuremberg Code*: Only advocates that clinical trials should yield fruitful results.

During the review of the clinical trial processes, there were terms and processes that were unique to clinical trials but appear to be aimed at managing the clinical trial promise. These were:

Beneficence: Beneficence refers to the ethical obligation to maximize benefit and to minimize harm (WHO, 2005). This principle gives rise to norms requiring that the risks of research be reasonable in the light of the expected benefits and that the research design be sound (WHO, 2005). The principle of beneficence bears a close relationship to the GCP requirement that research should be justified on the basis of a favourable risk/benefit assessment as stated in the Belmont Report shown in table 6 (WHO, 2005).

Endpoint: An endpoint is the clinical or surrogate item that is being assessed to determine whether the drug or intervention is effective (Bairu and Chin, 2012). Early in the development and evaluation of an intervention, regulatory agencies use endpoints to determine the safety and biological activity of an intervention and later on, endpoints help investigators to decide whether a drug provides a clinical benefit (Bairu and Chin, 2012). A good clinical endpoint should be

clinically relevant, reflect the overall disease being treated, informative, sensitive, discriminating, reliable and robust (Bairu and Chin, 2012).

Interim analysis: Interim analysis is a process of examining and analysing data as it accumulates during a clinical trial, either formally or informally, during the conduct of the clinical trial (Chow and Liu, 2008). Interim analysis seeks out errors, safeguards the blinding of a study and assesses safety (Chow and Liu, 2008).

4.3.2 The online survey

When analysing the responses to the survey, it was important to keep in mind that 74% of the respondents admitted to lack of familiarity with BRM and this was a possible limiting factor in providing specifics HIV clinical trial BRM and BRM processes. Other questions were included in the survey to still put piece together how HIV clinical trials management deals benefits even if they are unfamiliar with formal BRM and BRM processes.

4.3.2.1 Do clinical trials achieve what they set out to?

There was an overall confidence from the respondents that clinical trials delivered on their intended purpose with only 3 respondents out of the 19 giving a percentage estimate below 50% as shown in figure 18.

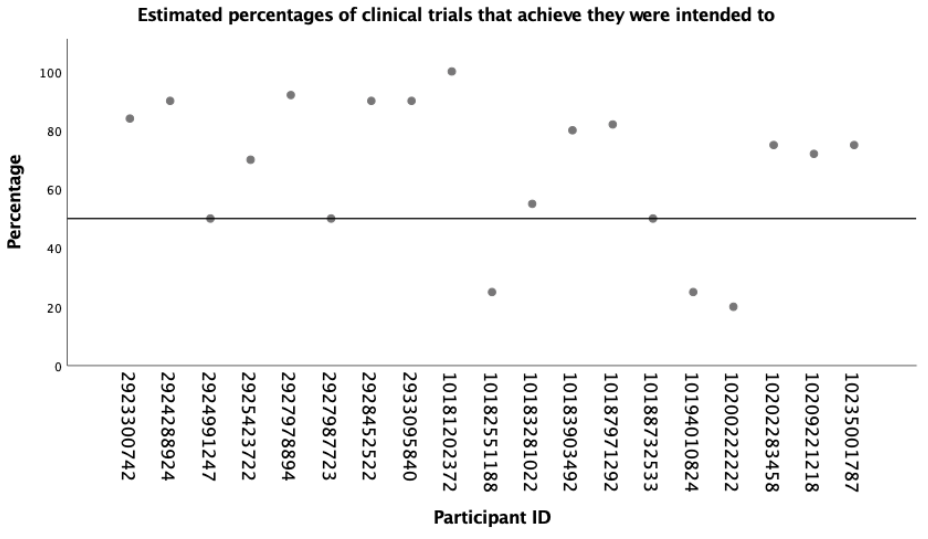

Figure 18 Confidence in clinical trials achieving their goals.

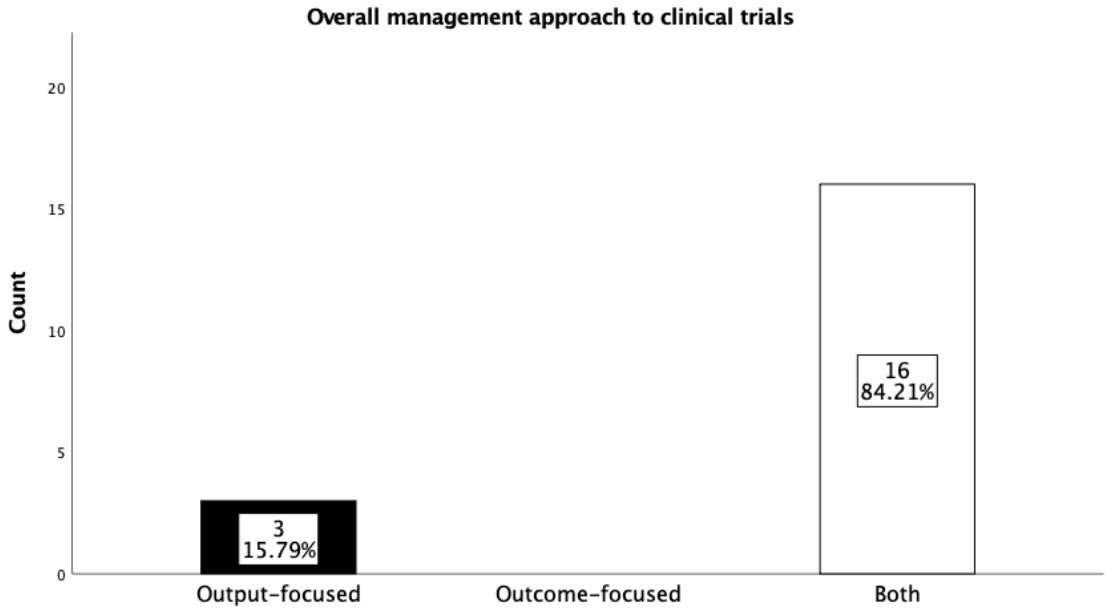

Figure 19 The interpretation of the focus of the general management approach to managing HIV clinical trials by the respondents.

4.3.2.2 Management Approach

Figure 19 shows that 84% of the respondents stated that the overall management approach in HIV clinical trials is focused on both outputs and outcomes. The other 16% of the respondents believed that the general management approach was focused only on outputs.

4.3.2.3 Accountability for realizing benefits and sustaining them?

The principal investigator was identified as the stakeholder in clinical trials that is responsible for the realization and sustaining benefits by 53% of the respondents as shown in figure 20. Other respondents mentioned either the project manager, the data monitoring committee or IRB as the stakeholders accountable for benefits realization.

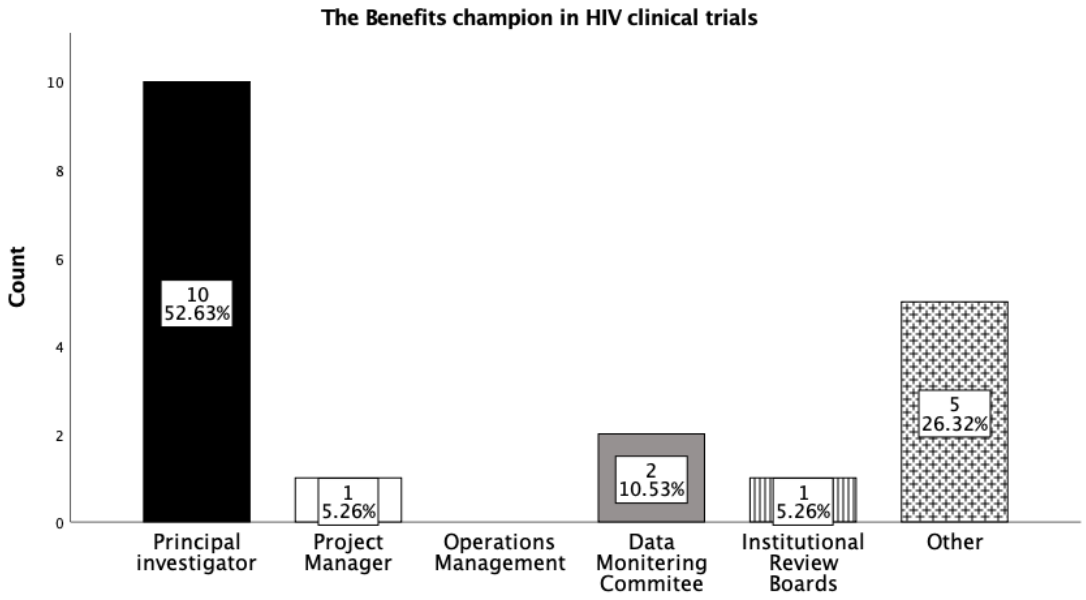

Figure 20 The stakeholder charged with championing and sustaining benefits

Some of the detailed responses to the question of who was accountable for realizing and sustaining clinical trial benefits, are listed below.

"They are spread out and performed by different people."

"All of the above and the team."

"It is multiple stakeholders and teams from project managers to principal investigators."

"All staff working to implement the trial."

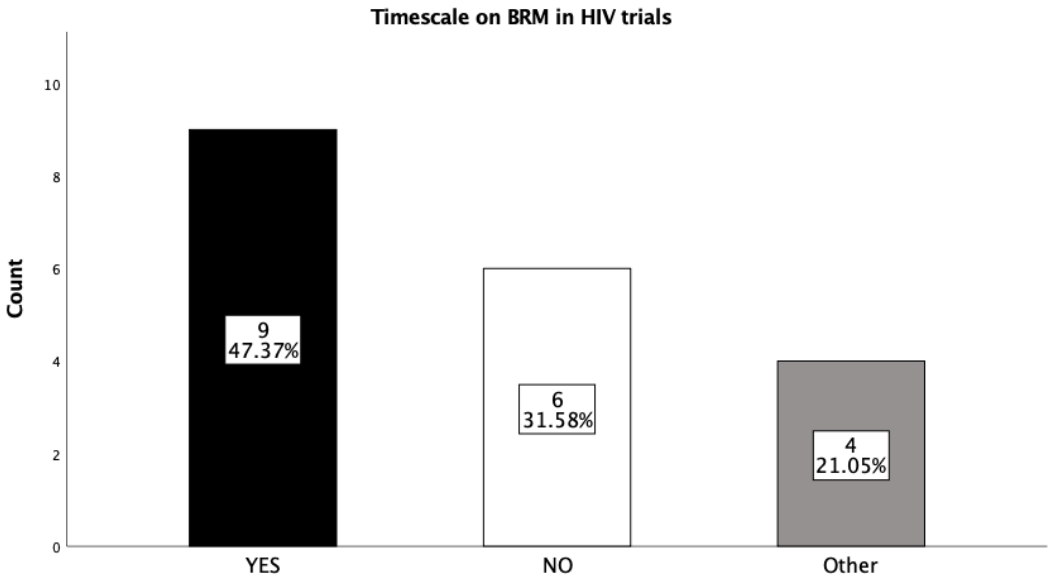

Figure 21 Establishing whether there is a set timescale to realizing HIV clinical trials benefits

4.3.2.4 Benefits timescale?

When assessing whether a time frame was placed on the realization of HIV Clinical trials benefits, 47% of the respondents claimed that there was a set time for benefits realization as shown in figure 21. Those that said there no set time were 32% of the respondents with the remaining 21% claiming to either not know enough or that there are other variables to factor in. these were some of the comments from the respondents:

"The timescale is based on the endpoint results and the decision by the data monitoring board."

"I don't know."

"Benefits are realized through peer reviewed publication and meritorious publications and data could lead to new drugs and standards of care."

4.4 How do the current practices compare with those described in the literature?

4.4.1 Literature

Table 6 was designed with reference to what is known in published work about benefits management processes. Similar processes or aspects of clinical trials guidelines that appeared to match those in BRM literature, were populated in table 6. Several of the reviewed guidelines appeared to aspects that fit into benefits management plan, benefits identification, benefits planning and benefits measuring. The review showed that the guidelines lacked aspects of actual benefits realization, benefits review and benefits reporting or follow-up.

4.4.2 The perception of current practices by the respondents

The majority of respondents claimed that the processes used to manage benefits of HIV clinical trials are below where they need to be as should in figure 22. There was 26% of the respondents who felt that the processes used to manage benefits of clinical trials were on the same level as other industries. An equal 26% of the respondents excused themselves from commenting due to their lack of knowledge of BRM.

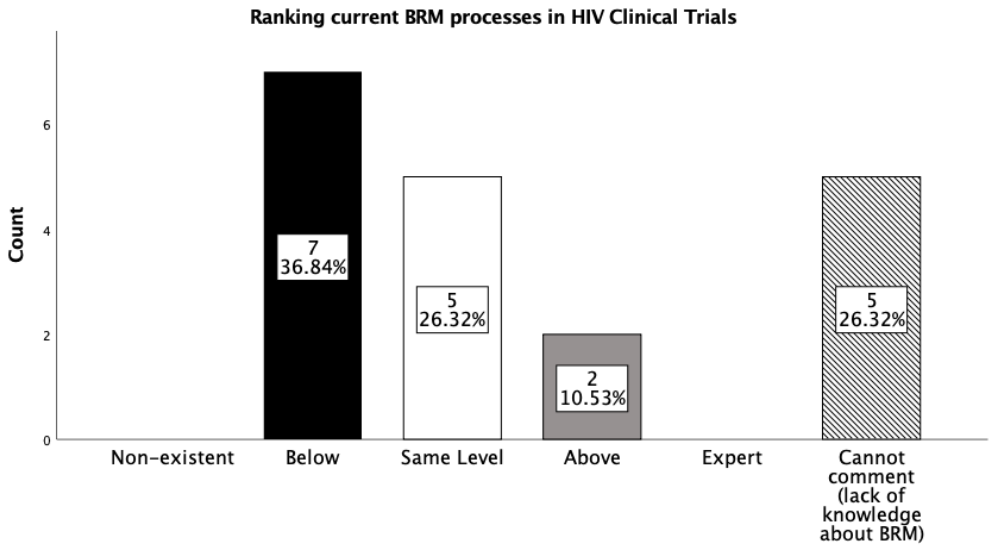

Figure 22 The respondents ranked the benefits management processes currently used in managing HIV clinical trial benefits.

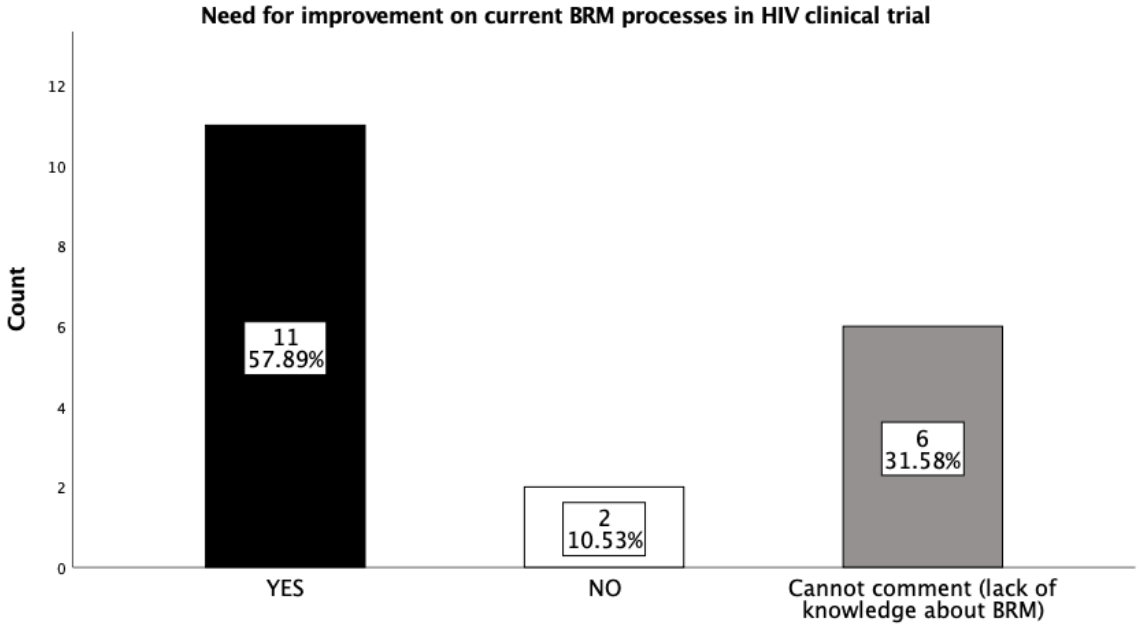

Figure 23 The respondents were asked whether they felt there was a need to improve the processes currently used to manage benefits of HIV clinical trials.

Of the 19 respondents, 11 of them were open to improvements being added to the current ways of managing HIV clinical trials benefits as shown on figure 23. Below are some of the additional comments by the respondents with regards to the need for improvement of processes in HIV clinical trials.

"Overall, preventive HIV vaccine trials offer few benefits to the individual participant. The benefits are largely for the scientific field, which stands to learn from the trial. Until we actually have a licensed vaccine that can be deployed, the benefits will continue to be limited."

"We do need to improve our processes."

"Always room for improvement."

5 Discussion of findings

This chapter discusses the finding of this study that were presented in chapter 4. This chapter looks to add details and context to the study findings.

5.1 Interpreting the results

It is important that there is contextualized and cautious interpretation and generalization of the research findings of this study. The findings from the review of the guidelines and literature can be generalized as these documents are applicable in most clinical trials not just HIV clinical trials. There should be limited generalization of findings from survey part of this research as there were concerns because of the low response rate obtained (Radhakrishna and Doamekpor, 2008). This is to avoid reaching conclusions using findings that are vulnerable to both sample error and sample bias due to the low response rate (Nulty, 2008).

The low response rates may have been due to the structure of the questionnaire. Even before respondents decide whether they will participate in the survey or not, the response rate is significantly influenced by factors such as subject, formatting and length of the survey (Nulty, 2008; Fan and Yan, 2010). Numerous attempts were made as proposed by Fan and Yan (2010) and to the best abilities of the researcher, to improve the quality and structure of the survey in order to develop a survey with a satisfactory response rate. There is lack of consensus in the literature about an exact number that is considered a satisfactory response rate because little is known about whether non-respondents differ from respondents (Radhakrishna and Doamekpor, 2008; Fan and Yan, 2010). Had the response been 100%, the question of generalizing the findings does not arise because everyone responded (Radhakrishna and Doamekpor, 2008). As soon as the response is not 100% and is low, the questions of why some stakeholders did not respond comes up and whether the data are only valid for those that responded (Radhakrishna and Doamekpor, 2008). The survey results obtained from this small sample are not likely to be an indication of what the population would have said but should still be considered by future related studies.

5.2 Management Approach

What is apparent and central to the management approach and documentation of clinical trials is the heavy focus on ethics and the safety of all the human participants. This is mostly based on hard historical lessons. The Nuremberg Code, for example, was formulated in 1947, in Nuremberg, Germany, by American judges sitting in judgment of Nazi doctors accused of conducting murderous and torturous human experiments in the concentration camps (Shuster, 1997). Informed consent was the core of the *Nuremberg Code* but it served as a blueprint for today's principles that ensure the rights of subjects in medical research camps (Shuster, 1997). *The Declaration of Helsinki* serves as a guide on the obligations of physician-investigators to research subjects and focuses on the protection of subject rights and to those involved in medical research that involves humans (Shuster, 1997; Otte *et al.*, 2005). It is for these reasons that designing, conducting, recording and reporting trials that involve the participation of human subjects is mostly focused on protecting the rights, safety, and well-being of trial subjects (Otte *et al.*, 2005).

The GCP only controls scientific experimentation and leaves unaddressed most management issues (Bongiovanni *et al.*, 2015). Complexity in management is a result of sizeable projects that have a high degree of uncertainty, have numerous interacting elements and apply new methods (Vidal and Marle, 2008). Clinical trials involve recruiting large patient sample sizes, managing multisite teams, inclusion or exclusion criteria, scheduling, collaborations and unpredictability clinical outcomes and all these give rise to complexity (Bossert *et al.*, 2002). The focus of a project plan and management should be placed on the connection between project goals and the purpose behind those goals (Hubbard, 2000). Due to the uncertainty of clinical trials, it is hard to make any guarantees on benefits even when the trial is efficiently managed as the trial may still not produce the desired outputs and not fulfil the purpose (Farrell, 1998; King, 2000; Farrell *et al.*, 2010). In other words, the “efficacy” of an experimental intervention (i.e. a measure of the success of an intervention in an artificial setting) may not translate into its “effectiveness” (i.e. a measure of its value applied in the “real world”) (Umscheid *et al.*, 2011).

Too much focus on delivering the classic project iron triangle performance measures (cost, time and scope) creates an "output-focused" mentality which limits the effectiveness of the organisation to realise benefits from its projects (Chih and Zwikael, 2015). The respondents believe that the management approach to HIV clinical trials is focused on both outputs and outcomes. Which means management seeks to put in place processes that are orientated on deliverables, efficiency as well as benefits and value. The management approach to clinical trials, according to the survey, is therefore focused on running and managing clinical trials as efficiently as possible at the same time getting as much value out of clinical trials as possible. This management style implies that that there is a possibility that benefits management processes exist in clinical trials or that there is potential for implementation of BRM processes if they already do not exist.

BRM is an approach for the optimization or maximization of benefits from organizational change programmes (Sapountzis, 2013). To realize benefits, changes have to happen from the top through effective governance. The respondent in this study are in a great position to influence BRM in clinical trials as the majority of them indicated in figure 15 that they are involved in the strategic planning of clinical trials. ul Musawir *et al.* (2017) acknowledges that interaction between project governance and benefit management process is more complex than a simple cause-and-effect relationship but project governance creates the roles, responsibilities, and accountabilities that enable benefit management. The insertion of changes within organizational processes does not automatically result in benefits but benefits arise when the people in the organizations embrace the changes in their business processes (Doherty *et al.*, 2012; Sapountzis, 2013).

5.3 BRM processes in clinical trials

Throughout this investigation, several clinical trial documents and guidelines were scrutinized but BRM processes in HIV clinical trials. People who work and manage clinical trials were used as sources of information in exploring benefits management in clinical trials. The spread of expertise

and the involvement in clinical trials by the survey respondents were broad and diverse enough to offer confidence in their observations and comments. The respondents were at different levels of management, different skillsets, played different roles in clinical trials and worked for different HIV trials and appear to have been involved in benefits planning, identification and putting together a benefits plan of their perspective clinical trials.

This study looked to unearth BRM processes in clinical trials and establish an understanding of how HIV clinical trial benefits were managed and realized. None of the documents that were reviewed in this study were solely focused on benefits management. There was several mentions of benefits and their importance but not BRM processes. The guidelines highlighted the importance of risk-benefit assessment of every clinical trial but did not give specifics on how to go about conducting the risk-benefits assessment. Even though there was limited familiarity within clinical trial management with BRM and BRM processes, there was high confidence levels that clinical trials deliver what they intend to achieve as shown in figure 18. This study was not able to explicitly locate BRM processes in clinical trials however, the positive outlook on clinical trials achieving their goals by the respondents implied that good management practices were in place somewhere.

What was apparent was that benefits and benefits assessment were treated as ethical issues. According to the Belmont Report, the term "benefit" is used in the clinical research context to refer to something of positive value related to health or welfare (WHO, 2005). Emanuel (2000) pointed out that it is an ethical requirement that potential benefits of a trial must always be higher than potential risks posed by the clinical trial. Successful clinical trial findings are those that fit the principle of generalizability which dictates that the findings must be applicable to clinical practice in the "real world" (Farrell *et al.*, 2010; Umscheid *et al.*, 2011).

5.4 Comparisons of BRM processes

It was worth comparing of how clinical trial benefits were managed to how IT/IS and/or general BRM literature suggests project benefits should be managed. Below are some of the common practices of BRM and what are referred to as BRM pillars.

Strategic fit: Benefits have to align with the organization's overall strategy (Chih and Zwikael, 2015; Mossalam and Arafa, 2016). Benefits arise when changes are introduced through effective governance and enable organizations do things differently (Peppard *et al.*, 2007; Mossalam and Arafa, 2016). Realistic delivery methods for the project under analysis will lead to success given the context in which the organization is operating and its constraints (Chih and Zwikael, 2015; Serra and Kunc, 2015; Mossalam and Arafa, 2016). As 74% of the respondents were involved in the strategic planning of the respective clinical trial, they would be in a position to suggest and implement ways to align clinical benefits with the overall strategy.

Planning: BRM literature states that to deliver the project promise, the first step is for an organization to move away from an output focused style of management to a benefit orientated style of management (Chih and Zwikael, 2015). An overwhelming 84% of the respondents indicated that the style of management in clinical trials was both output and outcomes focused as shown in figure 19. It is important for a project to start with the end in mind by noting its expected outputs, outcomes, and benefits in the business case (Serra and Kunc, 2015; Mossalam and Arafa, 2016). The benefits must be measurable which would mean that each benefit has to have a baseline (Chih and Zwikael, 2015). The benefits planning in clinical trials should be included in the trial protocol as the trial is developing. Most of the respondents said that they were involved in the planning of their respective clinical trials that worked on which implied that they are aware and were influential on the general planning of clinical trials including benefits planning.

Benefits identification: To direct the identification of benefits, principle 3 of the W.H.O states that before research involving humans is initiated, foreseeable risks and discomforts and any

anticipated benefits for the individual research subjects and society should be identified (WHO, 2005). There are parts of the process however, that require refining such as parameters used to identify and classify direct benefits need further clarification (Koonrungsesomboon *et al.*, 2016). Tumor shrinkage or remission, an extension in life expectancy of patients, or an improvement in the patients' quality of life in cancer trials can be considered as direct benefits but there are disagreements in the industry (Koonrungsesomboon *et al.*, 2016). The guidelines documents and the respondents all clearly acknowledged the importance of managing clinical trial benefits by identifying and assessing them.

Benefits Review: Project outputs and outcomes are frequently reviewed and realigned to the current expectations (Serra and Kunc, 2015). For tracking purposes, it is important for each benefit to have an owner that is responsible for that benefit (Lin and Pervan, 2003; Chih and Zwikael, 2015). In clinical trials, the overall responsibility for delivering the trial lies with the principal investigator and this would explain why the principal investigator was selected by the majority of respondents. (Goodarzynejad and Babamahmoodi, 2015). Other respondents named five other stakeholders as the ones that are supposedly championing BRM besides the principal investigator. It might be beneficial of adopt this approach of spreading out the BRM accountability per benefit to several people enable following up on benefits and sustaining them.

Benefits Realization: Although benefits are not the only criteria to evaluate project success, they are a measurement of how valuable a project is (Serra and Kunc, 2015). Project outcomes are monitored by the organisation after project closure in order to ensure the achievement of all benefits expected in the business case (Serra and Kunc, 2015). There is often a lag in benefits accumulation after the implementation it which means the outcome monitoring continues until each of the expected benefits has either been achieved or it is clear it will not materialize (Peppard *et al.*, 2007). Clinical trials can run for years and it is important to maintain and update a list of realized and anticipated benefits as way of keeping track of them. The respondents believed that benefits are realized when the intervention is licensed or through peer reviewed publications. IT/IS literature highlights the importance of a timescale for BRM purposes (Chih and Zwikael, 2015). A combined 10 out the 19 respondents said that there was no timescale to

benefits management in clinical trial and/or it is no easy to have a timescale. This brings into question the efficiency and accuracy of the processes that currently exist in clinical trials especially when following up on benefits once the clinical trials has reached completion.

Benefits review: In order to show added value, benefits must be measured in a systematic manner (Ashurst *et al.*, 2008). It is therefore important that planned benefits have to be monitored so that they are not lost as the project continues (Sapountzis, 2013). It is also worth pursuing additional benefits that may arise as the project progresses (Sapountzis, 2013). Principle 4 of the WHO states that research involving humans should be initiated only if the anticipated benefit(s) for the individual research subject and society clearly outweigh the risks (WHO, 2005). Principle 8 of the WHO states that research involving humans should be continued only if the benefit-risk profile remains favourable (WHO, 2005). This makes risk-benefits analysis for evaluating clinical trial benefits very important.

The data monitoring committees (DMCs) or data and safety monitoring boards (DSMB) play a critical role in the conduct of clinical trials by assessing the risks and benefits of an intervention as data accumulate (DeMets and Ellenberg, 2016). Monitoring by the DMCs is motivated primarily by an ethical imperative to prevent dangerous outcomes by stopping the trial early or to make the superior treatment available as soon as the evidence is definitive (DeMets and Ellenberg, 2016). Numerous complex statistical methods are used to assess the progress, success or failure of the trial. This is done by comparing the test group results with the placebo group and using the differences to make an assessment (Chow and Liu, 2008).

The is however, documented absence of clear criteria for assessing the risk-benefit ratio and this is a weakness in the IRB review process with some members of the IRB having been shown to not be fully competent in carrying out such evaluations (Van Luijn *et al.*, 2007). In order for a study to be approved by the IRB, the risk-benefit ratio must, in the IRB's opinion, be favorable, in balance, or proportional (Van Luijn *et al.*, 2007). This assumes that IRBs are sufficiently aware of which risks the medical research community and society, in general, find acceptable in relation

to which benefits (Van Luijn *et al.*, 2007). The extent to which this assumption is justified in practice is open to question, especially considering the vague description of this requirement in the various regulations (Van Luijn *et al.*, 2007).

5.5 The need for management improvements

Studies have shown inadequacies in how some clinical trials are conducted, managed and reported (Umscheid *et al.*, 2011; Smyth *et al.*, 2015). A sound scientific basis and a well-structured protocol can answer clinical questions but in the presence of inept management, successful delivery of a trial is unlikely (Farrell *et al.*, 2010; Goodarzynejad and Babamahmoodi, 2015). Once an intervention is approved, a phase IV trial should be conducted to evaluate adverse reactions and effectiveness when administered to the general population (Umscheid *et al.*, 2011). The literature suggests that less than half of such studies are actually completed or even initiated (Umscheid *et al.*, 2011)

There is an agreement in literature that the approach to running clinical trials requires an approach reform (Macleod *et al.*, 2014; Borgerson, 2016; Ioannidis, 2016). This thinking follows the continuous improvement philosophy which promotes on-going improvements that involves everyone in the organization and on all fronts (Thorp, 1999; Sapountzis, 2013). There are those who have recommended the application of project management in clinical research (Siegfried *et al.*, 2010; Payne *et al.*, 2011; Aghayan *et al.*, 2014; Goodarzynejad and Babamahmoodi, 2015). Payne *et al.* (2011) insisted that the use of project management increases the effectiveness of health and medical research projects as well as communication and teamwork within those projects. There also those who are specifically proposing development of a value culture in clinical research by integrating benefits with performance management and managing benefits from a portfolio perspective (Mossalam and Arafa, 2016). An integrated management model that merged existing project management and benefits management processes has been shown to increase the likelihood of projects achieving organisational goals, both in relation to IT and

general investments (Ward *et al.*, 1996; Lin and Pervan, 2003; Ward and Daniel, 2006; Mihić *et al.*, 2012; Breese *et al.*, 2015; Serra and Kunc, 2015; Mossalam and Arafa, 2016).

Clinical trials are intricately detailed and complex projects that need to be completed according to stringent global regulations and standards, and for a trial to be effective, multiple skill sets and strong hands-on management are essential (Bairu and Chin, 2012). There is a clear need for changes in the management approach of clinical trials to not only deal with increasing complexity and limitations, but also to improve the chances of clinical trials benefits realization. It is important for clinical trial management to adopt BRM "mentality" that focuses on factors that are required to realize the benefits from the projects (Breese, 2012; Chih and Zwikael, 2015).

Keeping in mind that Shenhar and Dvir (2007) pointed out that the 'one size fits all' approach to managing projects was not universally successful, the recommended management reforms in this study are not failproof but are believed to increase the odd of benefits realization. Koonrungsesomboon *et al.* (2016) highlighted that there is a need for a structured approach for assessing the clinical promise of new interventions. The first obvious limitation of benefits management in HIV clinical trials is that there were no documented processes, at least as far as this study could establish. Once the formal incorporation of BRM is adopted in clinical trials, it is important to ensure that these are visible to all those that are involved in the management of clinical trials. This will improve the understanding and/or awareness of the processes and therefore enable their implementation. HIV clinical trials should maybe adopt the practice of having a benefits champion that is used in IT/IS. This approach spreads out the BRM accountability per benefit to several people to enable benefits follow up and sustainability. The IRBs and DMCs/DSMBs should also have an increased role in benefits management (Umscheid *et al.*, 2011).

From 1999 to 2005, the total procedures per trial protocol increased by 65 percent, with unique procedures per trial protocol increasing by 46 percent (Bairu and Chin, 2012). The findings from this study, have led to the proposal of some key protocol adjustments. One such proposal is to

adjust the adjusting the 12 golden rules of GCP by including application of benefits management as one of the rules. The CONSORT and SPIRIT statements as well as how clinical trials are reported is also another proposed adjustment. When organizations embrace changes in their business processes, the chances that benefits arise, are increased (Doherty *et al.*, 2012; Sapountzis, 2013).

5.6 The utility of BRM thinking in clinical trials

As a relatively experienced life scientist with some understanding of how clinical trials work, incorporating management techniques to improve outcomes of clinical trials would be an essential undertaking. This work is no way comprehensive enough to draw very strong conclusions or propose massive process changes in clinical trials. It can however be used as a basis for a more comprehensive and unrestricted study into potential applications of BRM in clinical trials. Mossalam and Arafa (2016) proposed a benefits realization management process compatible with the process groups of the Project Management Institute (PMI) body of knowledge which will enable organizations to cascade responsibilities of delivering values to the project manager level. To activate this concept, a strong governance system should be in place to manage benefits effectively (Mossalam and Arafa, 2016).

BRM is a key aspect of project management that can possibly improve the delivery of the clinical trial promise. At the moment, this study showed that BRM in not a distinct or formal practice in clinical trials management although aspects of benefits management exist in current clinical trial processes. An immediate recommendation would be an assessment of the effects of formally adding BRM practices to clinical trial management using a case study approach. This study simply complements existing literature that project management skills are needed in clinical trials and should be added to existing clinical trials management processes (Siegfried *et al.*, 2010; Payne *et al.*, 2011; Aghayan *et al.*, 2014; Goodarzynejad and Babamahmoodi, 2015). The expectation would be that BRM processes improve the identification of clinical trial benefits, improve the execution of benefits realization plans while enabling continuous tracking of all clinical trial benefits during and well after the clinical trial. BRM will then contribute to increased chances of

achieving the clinical ethical requirements. Tracking the benefits will help keep the equipoise intact and with the principles of beneficence and maleficence in mind, benefits will then be maximized while possible harms are minimized.

This work although basic and preliminary, could be used as a foundation to motivate increased BRM visibility and incorporation of BRM processes into in clinical trials management. This would improve the delivery of benefits ensure that no benefits are missed or mismanaged throughout the duration of the clinical trial.

6 Conclusions and suggested future research

This chapter summarizes the more significant findings from this study. This chapter also points out the study limitations and makes recommendations for related future research.

The main takeaway from this study was that BRM processes are not readily visible or documented in HIV clinical trials. The bulk of the focus in the guideline about management of clinical trials appeared to be on human safety and risks of clinical trials which results in reduced prioritization on management of benefits. Recent growth in the clinical trial industry and the increasing complexity of clinical trials, warrants adjustments to the approach. This study proposes a more formal BRM approach to HIV clinical trials from the start of the clinical trial until some significant time after the clinical trial has been closed off.

The current state of general management in clinical trials can ease the introduction of BRM into clinical trials. The management approach is already orientated toward both deliverables and value. Most of the people involved in management are included in strategizing and are highly confident in that clinical trials deliver their promises. The established need for improvement can be addressed by incorporating and promoting application of formal BRM processes. Current clinical trial processes that are used to set and evaluate endpoints, apply interim analysis methods and assure beneficence, should be incorporated into formal BRM processes in a similar way to what was proposed by Mossalam and Arafa (2016). Other approaches used in other industries that should be adopted include the allocation of benefits realization responsibilities and starting with the end in mind.

Undoubtedly, there are better ways in which the literature and guidelines review could have been conducted. The search for keywords that are relate to BRM in clinical trials documents can be improved. Computational logarithms would probably be more efficient with such searches. The ability to execute some of these searches was beyond the skills level of the researcher. The search was manual with basic in-document program searches of only documents known to exist

by the researcher and also accessible to the researcher. One other limitation with the review was that some of guidelines were worded in formal law terminology that could have been missed by the researcher. The response rate to the survey was very low and this forced a change in the focus group. As a way to narrow down the sampling and easy access to some clinical trials managers, this study originally considered focusing only on HVTN trials, but some people contacted to participate in the survey indicated that were uneasy responding without the approval of the HVTN leadership, if at all. The study was therefore forced to widen the search for respondents to all those who are part of any HIV clinical trial. There was also a possibility some of the responses may have been tainted by bias as some of the people who currently manage clinical trials, would not want to appear incompetent or imply that their work was futile. This limitation could be addressed by further widening the type of clinical trials to all clinical trials as a way to get a more comprehensive respondents' analysis.

A potential worthwhile future study could be that of a long-term nature looking into the potential effects of BRM processes on clinical trials. An alternative future study could adopt the case study approach where several people who are manage clinical trials are trained in benefits realization, given a chance to apply the BRM processes over time and the impact assessed. If the impact of BRM in other industries is anything to go by, there is a chance that formally incorporating BRM in HIV clinical trials, could increase the chances of realizing clinical trial benefits.

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8 Appendix A

Table 7 Schools of thought of research

	Positivism	**Post-positivism**	**Interpretivism**	**Critical theory**
Ontology	Static and fixed, overarching objective truth	Static and fixed; Overarching objective truth	Subjective and changing; No one ultimate truth	Objective but truth is continuously contested
Epistemology	Objective, Generalizable, knowledge can be neutral or value free	Objective, world is not fully accessible, Seeks to establish 'probable' truth	Subjective, multiple and diverse interpretations, no one ultimate or 'correct' way of knowing	Co-constructed between individuals and groups, continuously under revision
Methodology	Discover what exists through prediction and control, deductive, uses scientific method to develop abstract laws to describe and predict patterns, Looks for causality and fundamental laws	Develop knowledge through the falsification of hypotheses, Emphasis on well-defined concepts and variables, controlled conditions, precise instrumentation and empirical testing	Focus on understanding, inductive reasoning, Meaning is constructed in the researcher-participant interaction in the natural environment, Gathers diverse interpretations	Focus on emancipation, Research is used to envision how things could change for the better, seeks representation of diverse and under-represented views, continual redefinition of problems and cooperative interaction
Methods (Techniques used to gather information)	Quantitative methods, statistical testing of hypotheses	Quantitative and qualitative methods	Qualitative methods	Both quantitative and qualitative methods

Source: *Bunniss and Kelly (2010)*

9 Appendix B

The Questionnaire

- Thank you for agreeing to respond to this questionnaire.
- The purpose of this research is to explore project management processes used in managing clinical trials with specific focus on benefits realization management (BRM). This will be done by reviewing documented guidelines on running and managing clinical trials as well as online surveys with individuals involved in the management of clinical trials.
- Please note that you will remain completely anonymous and your responses will be kept strictly confidential. You are free to withdraw from the process at any time.

1. Were you as (principal investigator/trial manager/project manager/clinical trial coordinator/other) involved at the strategic and planning level of clinical trial?

2. What would you say is the current management approach of clinical trials?
   - A- Output-focused (deliverables and efficiency-orientated)
   - B- Outcome-focused (benefits-value orientated)
   - C- Both

3. How familiar are you with Benefits Realization Management (BRM)?
   - A- Never heard of it
   - B- Familiar with it but I have not applied it in any project
   - C- Familiar with it and apply it on all projects

4. Are there comprehensive benefits management processes (Plan, Identify, Realize and Review) in HIV clinical trials?

5. Using any number between 1-5 (1 being the lowest and 5 the highest), where would you rank clinical trials BRM processes compared with those described in the literature:

   1 = Non-Existent

   2 = below

3 = same level

4 = Above

5 = Expert

6. In your estimation, what percentage of clinical trials achieve what they set out to achieve?

7. Who is accountable for realizing and sustaining clinical trial benefits?

8. Is there a timescale by which individual benefits are expected to arise?

9. Would you say there is a need for improved processes in benefit realization management in clinical trials?

10 Appendix C

Key Trial Activities

At the beginning of a clinical trial, sponsors and investigators develop/formulate a feasible and scientifically valid set of important clinical/medical questions to be addressed by the intended clinical trial (Chow and Liu, 2008). Then the following steps are followed.

1. Develop trial protocol
    - Sponsor and PI – risk identification, study design, control groups, statistical methodology
2. Develop SOP
    - Sponsors – clinical investigation- IRB monitors: responsibilities, records, methods, standardized activities, monitoring and auditing
3. Develop Support systems and tools
    - Brochure, logs, study flow sheets, computers
4. Generate and receive trial documents approval
    - Finances, informed consent
5. Select trial sites
6. Ethics committee review and approval of Protocol (Prior to enrolment)
7. Review by regulatory authorities
    - National/regional/local law and regulations
8. Enrolment of subjects
9. Handling of product to be tested
10. Conduct the trial
11. Safety management and reporting
    - Safety, adverse events, serious/life threatening unanticipated events
12. Monitoring thee trial
    - Conduct, blinding, endpoints of the trial, risks, adherence to the protocol, data entry and quality control.
13. Managing trial data
    - Make sure data are complete, reliable and processed right.
14. Quality assurance of trial performance and data
    - Study monitoring
    - Data management
    - During and at completion
15. Report the trial
    - Results described and summarized in study report (WHO, 2005).

11 Appendix D

Format and Contents of a Clinical Trial Protocol (Chow and Liu, 2008)

1. Protocol cover sheet
2. Background
3. Objectives

   Primary

   Secondary
4. Study plan

   Study design

   Subject inclusion criteria

   Subject exclusion criteria

   Treatment plan
5. Study drugs

   Dose and route

   Method of dispensing

   Method and time of administration

   Description of controls

   Methods of randomization and blinding

   Package and labeling

   Duration of treatment

   Concomitant medications

   Concomitant procedures
6. Measurements and observations

   Efficacy endpoints

   Safety endpoints

   Validity of measurements

   Time and events schedules

   Screening, baseline, treatment periods, and post-treatment follow-up
7. Statistical methods

   Database management procedures

   Methods to minimize bias

Sample size determination

Statistical general considerations

Randomization and blinding

Dropouts, premature termination, and missing data

Baseline, statistical parameters, and covariates

Multicenter studies

Multiple testing

Subgroup analysis

Interim analysis

Statistical analysis of demography and baseline characteristics

Statistical analysis of efficacy data

Statistical analysis of safety data

8. Adverse events

   Serious adverse events

   Adverse events attributions

   Adverse event intensity

   Adverse event reporting

   Laboratory test abnormalities

9. Warning and precautions

10. Subject withdrawal and discontinuation

    Subject withdrawal

    End of treatment

    End of study

11. Protocol changes and protocol deviations

    Protocol changes

    Protocol deviation

    Study termination

12. Institutional review and consent requirements

    Institutional review board (IRB)

    Informed consent

13. Obligations of investigators and Administrative aspects

    Study drug accountability

Case report forms

Laboratory and other reports

Study monitoring

Study registry

Record retention

Form FDA 1572

Signatures of investigators

Confidentiality

Publication of results

14. Flow chart of studies activities
15. References
16. Appendixes

12 Appendix E

Benefits Realization in Clinical Trials Study
(Consent Form)

The study explores project management processes used in managing HIV clinical trials with specific focus on benefits realization management (BRM). This study will establish awareness and application BRM frameworks within the HIV clinical trials as proposed in literature through semi-structured assessment of individuals involved in the management of clinical trials. The findings from this study will help in the improvement of BRM processes in clinical trials or serve as a guideline on how BRM can be incorporated into current management practices of clinical trials. This project is run by a master's student registered at the University of Cape Town. The student would like to ask you some questions to establish the existence and possible effectiveness of benefits management processes in HIV clinical trials.

Before responding, the student wants to make sure you understand the following information about the study:

- Your participation is entirely voluntary. You may refuse to take part in the questionnaire, and you may stop at any time if you do not want to continue. You also have the right to skip any particular question or questions if you do not wish to answer them.
- The time it takes to complete the questionnaire will vary depending on how many sections of the questionnaire are relevant to you, but the average amount of time is about 8 minutes.
- You have the right to ask questions at any point before or during the responding
- All information collected for this study will be kept strictly confidential. While the data collected will be used for research purposes, information that could identify you or your household will never be publicly released in any research report or publication.
- Your personal details will only be kept on record for instances whereby additional information may be required. However, we will ask your permission to participate in the survey again each time. Agreeing to participate now does not mean you have to participate in future surveys.

By signing below, you signify that you agree to participate in the study, and that your participation is entirely voluntary.

_____ _____
SIGNATURE: Participant DATE

_____ _____
SIGNATURE: Student DATE

If you have questions about this study or the research project you can call Molati Nonyane 071 887 0438 or molati.nonyane@gmail.com. This study has been reviewed and approved by the ethical review committee of the University of Cape Town (pending).