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# CHALLENGES FACING RESEARCHERS CONDUCTING CLINICAL TRIALS IN HIV PREVENTION IN SOUTH AFRICA: A FOCUS ON ADHERENCE.

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“Submitted in partial fulfillment of the requirements for the award of M.Sc. in  
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Challenges facing researchers conducting  
clinical trials in HIV prevention in South  
Africa: A focus on adherence.



## ABSTRACT

In clinical trials, adherence of the participants to the dosing instructions is a major challenge. Many researchers have identified medication adherence as a topic to further explore in order to obtain good, usable and reproducible results.

In order to gain an understanding of on-the-ground issues in clinical research a survey was conducted, isolating the issue of medication adherence among participants as a discussion point. The research was conducted specifically at clinical trial sites that are involved in HIV pre-exposure prophylaxis research. The survey was conducted at clinical trial sites across South Africa among health care workers in the clinical research sector. The principle issue to be identified was the perceptions of staff and researchers with regards to the current approach to adherence measurement and possible suggestions from them on future adherence interventions strategies.

This research was conducted as a qualitative analysis from February to March 2014. Eighteen responses were received. Among the respondents were investigators, medical officers, nurses and pharmacists. The results of the survey suggest that healthcare workers have a strong understanding of the importance adherence monitoring and intervention. They have many ideas on which measurement tools work and which don't, but most importantly feel that the self-report or interview techniques are the most useful. Researchers also feel that much more can be done in order to improve the perception of the clinical research institutes in the eyes of the community and that a more active role should be taken in the community in order to improve the acceptance of the participants to the use of the product.

The survey also highlighted the need for education of the participants and the need for a mutually trustful relationship between the participants and the researchers in order to gain help the participants overcome any issues that they have regarding the product and its use according to the directions. A few suggestions were forthcoming, to be

applied in the future when initiating clinical research in an area; such as cultural sensitivity and community acceptance.



## DECLARATION

I declare that this thesis I now submit for assessment on the program of study leading to the award Master of Science Pharmacy Administration and Pharmacy Policy Specializing in Regulatory sciences in has not been submitted as an exercise for a degree at this or any other college. It is entirely my own work and has not been taken from the work of others, save the extent that such work has been cited and acknowledged within the text of my work.

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Signed Deulman Dated 12 MAY 2014



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## LIST OF ABBREVIATIONS

AIDS – Acquired Immunodeficiency Syndrome

ARV – Antiretroviral

CAPRISA – Centre for the AIDS program of Research in South Africa

GCP - Good Clinical Practice

HAART –Highly Active Antiretroviral Therapy

PrEP – Pre-Exposure Prophylaxis

SRC – Setshaba Research Centre

UNAIDS –The Joint United Nations Program on HIV and AIDS

UWC – The University of the Western Cape

VIRA - Visual Inspection of Returned Applicators

WHO – World Health Organization

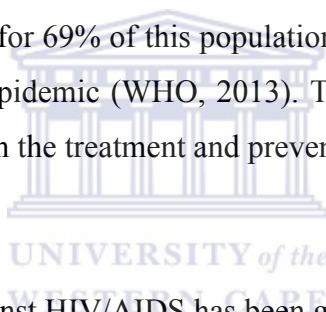
WRHI - Wits Reproductive Health and HIV Institute



# CHAPTER 1

## INTRODUCTION

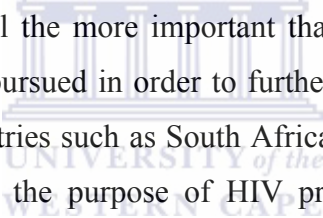
HIV/AIDS and its management has become one of the most popular topics of discussion the world over. From researchers to lay people, this epidemic has had an effect on every population in the world; and thus the global community is eagerly awaiting news of interventions that can change the destructive course of this virus. The following statistics illustrate, in an understandable manner, the impact that this virus has had on the African population in particular. The world health organization (WHO) has reported that the number of people living with HIV at the end of 2012 was 35.3 million; with roughly 2.3 million newly infected each year (WHO, 2013). Sub-Saharan Africa accounts for 69% of this population, making it the most prevalent region in the world for this epidemic (WHO, 2013). This makes sub-Saharan Africa the ideal location for studies in the treatment and prevention of HIV.



In South Africa, the fight against HIV/AIDS has been given a positive boost with new results showing that between 2004 and 2012 the number of newly infected persons per year has decreased by almost 30% (UNAIDS, 2014). Furthermore this report has stated that South Africa has the largest antiretroviral (ARV) roll out program in the world, with 2.2 million people currently having access to treatment (UNAIDS, 2014). This treatment is referred to as ARV treatment or alternatively as Highly Active Antiretroviral Therapy (HAART). It is due to this wide availability of treatment for HIV positive persons, that the population of South Africa is healthier, has more opportunity to live longer and has made progress in reducing the rate of new infections (Donnel et al., 2010; Grant et al., 2010).

From the above statistics it can be seen why it is becoming increasingly cost effective as well as convenient for large multi-nationals and aid organizations to use South Africa as a source of clinical research pertaining to HIV and other diseases. A part of

the reason for this is the large burden of HIV/Aids infection that is carried by the sub-Saharan continent. There is also a vast socio-economic gap between the rich and poor, which means that the population of poor persons are more willing to participate in any activity that would result in a better healthcare benefit as well as a monetary or other incentive (Wemos, 2013). There is also a great deal of scope for research in South Africa as high-skilled and research oriented personnel are widely available and due to socio-economic factors, treatment naive and willing participants are easy to recruit. Most of the participants are situated around large cities. They are young, healthy and eager to participate in research. Access to healthcare benefits that accompany participation in clinical trials is an added incentive. This healthcare standard is much better than would be expected from government facilities and thus coveted by most people; especially young females with many people are dependent on them for financial support.



This environment makes it all the more important that research into new treatment and prevention strategies be pursued in order to further curb the spread of this HIV, especially in developing countries such as South Africa. One of the products that are currently in development for the purpose of HIV prevention is the Pre-Exposure Chemoprophylaxis, using a single or multiple antiretroviral drugs in healthy HIV negative people to prevent acquiring the disease (Grant et al., 2005).

The success of anti-retroviral medications as well as pre-exposure prophylaxis (PrEP) measures in the treatment and prevention of HIV transmission is dependent upon the adherence of the patient to the product (Koenig et al, 2013). Adherence in pharmaceutical terms is the compliance of a subject/patient with the dosing regimen of the product that they are using. The Merriam-Webster dictionary describes adherence as “the act of doing what is required by a rule, belief, etc.”(<http://www.merriam-webster.com/dictionary/adherence>). The overall success or failure of the research study on a product is dependent on both the efficacy of the active components as well as the participant’s compliance with dosing regimens and the appropriate use of that product (Abdool Karim, 2010). This has been shown to be the case in many published articles from studies conducted on the effectiveness of

current treatment measures and future prophylactic options (Bangsberg et al., 2000; Hogg et al., 2002; Paterson et al., 2000; Simoni et al., 2006).

The measuring of adherence is a major portion of the data collected during a clinical trial (Simoni et al., 2006). In most cases self-report is used to collect the adherence data as well as one other method such as pill counts or CD4+ count measurements or other biological measurements (Chesney et al., 2010). Multiple adherence measurement tools are employed in clinical research and the data generated from these are used to interpret the findings of the trial and to validate data. It has been shown that adherence does impact the quality of data produced from a trial (Simoni et al., 2006; Koenig et al., 2013). Newer research results that show lack of adherence as one of the primary reasons for study failure have highlighted the need for research into interventions to improve adherence and thus more accurate representations of the efficacy of the products under study will be forthcoming (Weiss et al., 2008).

Therefore, it is important to investigate the barriers to good adherence and the possible ways to overcome them. This can be more reliably done by evaluating the issues from a perspective that is in touch with the everyday workings of the participants and their problems. These persons are most often the healthcare workers or clinical research staff that routinely interact with these participants and are able to create a relationship of trust between them and the participants in the research study.

The aim of this study is to evaluate the perceptions of adherence, its measurement and tools used to improve adherence, in the staff that work directly with clinical trial participants and are most often those that are able to influence adherence behaviors in these participants.

This study was conducted as a qualitative analysis of the perceptions held by the healthcare workers in the field of clinical research. The purpose of this was to obtain an idea of the current mindset of these professionals and as an extension, the mindset

of the participants in the trials. Furthermore it was conducted with the aim of garnering ideas from the ground level on what are the most challenging areas in clinical research and what are their ideas for strategies to overcome these challenges.

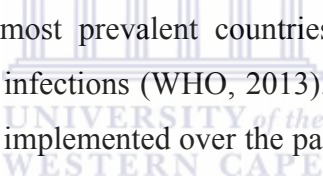
A qualitative analysis was used as the study design as it allows for a free-flow of ideas and information and brings forth the main issues at the forefront of the problem more easily. It is suggested that as a follow up to this study a similar study should be undertaken assessing the perceptions of the participants in clinical trials with regards to their own issues in adherence as to their opinions on what can be done further to help them. It would be very informative to gain an idea from the participants of their acceptance of assistance from the clinical research personnel and whether they feel satisfied with how things are being handled or not.



## CHAPTER 2

### LITERATURE REVIEW

A review of the literature that mentions the topic of adherence to Highly Active Antiretroviral Therapy (HAART) treatment and pre-exposure prophylaxis (PrEP) measures produces an extensive range of results spanning many years. The topic of adherence has been discussed from the inception of research into this field and therefore it is possible to say that due to this most of the methods currently in use for adherence measurement and improvement are tried and tested (Simoni et al., 2006). The purpose of this study is not merely to discuss these methods but also to ascertain the perception that healthcare workers in this field have of the issue of adherence and its management in a clinical trial setting.



South Africa is one of the most prevalent countries with regards to HIV/AIDS infection as well as new HIV infections (WHO, 2013). Success has been seen in the rollout of ARVs that has been implemented over the past few years (UNAIDS, 2014). Therefore, this environment is ideal for the study of new measures such as pre-exposure prophylaxis. It has been found in many previous studies conducted on PrEP measures (Weiss et al., 2008) that adherence to the treatment regimen is paramount in ensuring efficacy in all cases except the use of the irreversible surgery of male circumcision in which case adherence is calculated as 100% (Weiss et al., 2008; Koenig et al., 2013). This intervention, however, is entirely in the control of the male population, creating a need for interventions that can empower the female population in taking an initiative in HIV prevention.

In the clinical research setting, there are many challenges to acquiring good, reliable and beneficial data. Some of these challenges include budget limitations, participant recruitment and retention, community acceptance, and due to the length of time needed to complete the research, study fatigue. Of these challenges the one with the greatest impact and effect on healthcare workers is the issue of product adherence or

compliance. This has to be both measured and maintained at a high level throughout the trial and can put a strain on human resources.

Direct and indirect measurements of adherence can be found in the literature, which have been developed and analyzed. Direct measures are those that rely on biological sampling and measuring of drug levels or other biomarkers in these samples (Tolley et al, 2010). Indirect measures include pill and applicator counts, electronic monitors, diaries and questionnaires – self-reported or interviewer administered (Chesney et al., 2010). By far the most convenient, widely used and inexpensive method is the self-report method (Walsh et al., 2002).

Adherence monitoring is carried out in clinical research with the aim of gathering data for multiple purposes as apposed to adherence monitoring for patients on ARVs. Some of these include: determining the effectiveness of the product, as a support to trial results, to add to safety data and finally to understand the acceptability of the product and its use (Tolley et al., 2010). In the case of the current PrEP research most of the research participants are female as the intra-vaginal microbicide gels are to be used by the female population. The oral chemoprophylaxis measures are also geared towards the female population as they have been identified as a population in need of empowerment as far a decision making when it comes to HIV prevention measures.

Thus far, research into adherence and interventions to low adherence has mainly been carried out on patient groups that are HIV positive and thus on an ARV regimen (Haynes et al., 1996). Many of the strategies applied to this group can be applied to pre-exposure prophylaxis research cohorts, but there are psychological and motivational differences between the two groups, which translates to the need for adherence initiatives for pre-exposure prophylaxis to be innovative and tailored specifically taking this into account. The major concern for adherence in the clinical research group is that the motivation for adherence to dosing regimes and payoff for good adherence behavior is not visible immediately (Tolley et al, 2010). That is, in patients taking ARV's due to HIV infection, the motivation is good health, quality



and extension of life. Whereas is participants enrolled in PrEP clinical trials none of these motivations apply to such an extent. These participants are healthy and the aim is not to treat an infection but to prevent participants from acquiring it. The danger is not immediately apparent and the motivation therefore, not as great.

This however, does not mean that tools and methods used in patients that are currently taking HAART do not apply to PrEP. Continuous education and motivational interviews are just 2 of the methods mentioned in the literature which can be easily applied to the pre-exposure prophylaxis clinical trial setting (Olem et al., 2013; Holzemer et al., 2000). The most cost effective and currently widely used adherence measurement tool of self-report is both effective as a measurement tool and as an intervention strategy. During this process, information is being passed between the participants and the researchers and this enables the researchers to address many issues that arise immediately and reassure the participant in the same sitting. This however has a drawback as self-report and interviewer administered adherence tools are subject to bias from both the interviewer as well as the subject (Tolley et al., 2010). Often times it has been noticed that if a good rapport is established with the interviewer, the subject becomes eager to please and thus does not reveal all the fact and problems that they are encountering. This is an issue that should be addressed in a way that allows for a good relationship between the two but does not encourage dishonesty on the part of the subject either due to a willingness to please or a fear of disappointing the interviewer.

Another aspect to be discussed is that at present, most of the clinical trials in this field are either those studying oral chemoprophylaxis products or intra-vaginal microbicide gels. These two products have emerged as the front-runners for any pre-exposure prophylaxis regimens that may emerge in the near future (Grant et al., 2010; Abdool Karim et al., 2010). It is expected that in the future a vaccine will be developed and studied in but these interventions are currently pursued as the next best option.

While oral chemoprophylaxis trials are conducted on both male and female participants, the intra-vaginal gel is specific to women. Therefore these Clinical research trials have women-centric issues and sensitivities, which may influence their adherence. This gender distinction could be a contributing factor in the low adherence observed in these trials and should be investigated further in other studies.

When creating adherence intervention strategies, the literature has prescribed three points at which it can be incorporated. These are in the design of the trial, when screening and recruiting participants and while the trial is underway in response to adherence concerns (Tolley et al., 2010). The results that are discussed from this study can be implemented at any of these stages.



## CHAPTER 3

### MATERIALS AND METHODS/STUDY DESIGN

The study design that was used in this study is that of a qualitative analysis using a questionnaire with open-ended questions. These questions were designed so that ideas can be solicited from the participants as to their thoughts on the issue of adherence. The questionnaire was created using the online software SurveyMonkey.com and distributed in both electronic as well as hard copy formats to ensure that healthcare workers could easily complete it even if Internet accessibility was not available to them.

Questions in the survey were designed in order to gain an understanding of the ideas that prevail among staff working in clinical research with regards to adherence and its importance in the ultimate success of the research being carried out. It was also designed to encourage respondents to provide ideas, based on their personal interactions with participants, on how to address poor adherence. The questions were based on gaining information that would either support or reject current theories in the literature regarding adherence in the clinical trial participant population. A sample questionnaire has been attached in Appendix I.

Questionnaires were distributed to 3 clinical trial sites across the country and an expected number of approximately 20-25 responses. Due to ease of distribution, collection and processing of results, an online medium was chosen for the survey. This however, resulted in a smaller number of responses than anticipated as many of the clinical trial sites in South Africa do not have internet connectivity. The one site at which paper questionnaires were distributed was Setshaba Research Centre. This was possible as this particular site was easily accessible for the investigator whereas the others were too far away in order to allow hard-copy questionnaires to be distributed and collected.

The results (Appendix II) were then analyzed and processed using Microsoft Excel® to generate pie charts and graphs and the essay format data was analyzed by the investigator for common ideas and discussed below in relation to the literature. After the discussion, conclusions and recommendations were drawn up in order to guide future clinical researchers in this field.



## CHAPTER 4

### DATA COLLECTION AND ANALYSIS

This research project was initiated in response to a need to understand and gain information from healthcare workers, in clinical research, regarding their ideas on the problem of clinical trial participant adherence to dosage instructions. This research was conceptualized in order to gain ideas on adherence intervention strategies that will be practical and acceptable in order to implement them in ongoing clinical trials or as a guideline to researchers planning future clinical research.

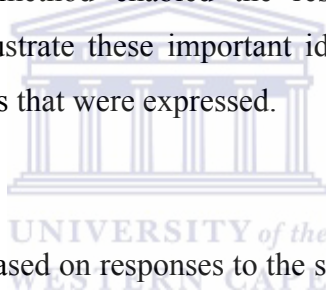
Due to the method of qualitative analysis used, a questionnaire was drawn up in order to collect the data required. This project was approved by UWC research ethics committee in compliance with Ethical standards after which data collection was possible. A disclaimer was added at the beginning of the survey to announce to any participant that the completion of the survey is voluntary and for research purposes only and if a participant refuses to complete it they are under no obligation.

Data collection and analysis were carried out using the SurveyMonkey.com website. Surveys were distributed on 13 February 2014 and data collection was stopped on 26 March 2014. Surveys were distributed to clinical trial sites across the country with an expected return sample of 20-25 answered surveys. Unfortunately as the time that was allocated for surveys to be completed and returned was short, only 18 responses were received.

During the data collection period, data was collected in online as well as paper formats. The hard copy surveys were entered into the software on the 26<sup>th</sup> March 2014, on the last day of the data collection period. After that data was analyzed and interpreted as discussed in the discussion and conclusion.

Contributing to the low number of responses is the issue of Internet connectivity at the clinical trial sites. Most of the sites that received questionnaires do not have reliable Internet access and therefore this made it difficult for the healthcare workers to complete the survey. Hard copy questionnaires were only available at one site i.e. Setshaba Research Centre, therefore it can be noticed from the results that most responses were collected here. This is a challenge for any research conducted in this manner and must be considered in the future so that study design can be altered to account for this.

Data was analyzed as is standard for a qualitative study (Taylor-Powell and Renner, 2003). Common ideas were grouped together and plotted on a bar graph. This was carried out in order to establish the number of respondents that had shared ideas and common perceptions. This method enabled the researcher to identify areas of particular concern and to illustrate these important ideas in a format that allows a reader to understand the points that were expressed.



The following discussion is based on responses to the survey that was conducted. The survey results were collated in Microsoft Excel<sup>®</sup>. These results are attached in Appendix II.

## CHAPTER 5

### DISCUSSION

#### QUESTION 1 – BIOGRAPHIC AND GEOGRAPHIC INFORMATION

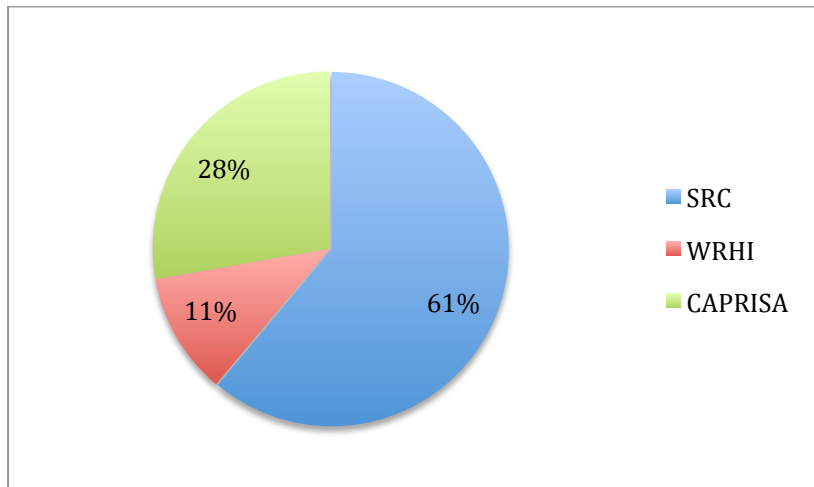
Healthcare workers from 3 clinical trials sites in South Africa completed the surveys that were returned. These include Setshaba Research Centre in Pretoria, Wits Reproductive Health and HIV Institute (WRHI) in Johannesburg and Centre for the AIDS Program of Research in South Africa (CAPRISA) in KwaZulu-Natal (KZN).

Most responses were received from SRC (11) with the least responses being from WRHI and a fair amount of response from CAPRISA. The drastic difference in response amount that was received from SRC is due to the event that hard copy questionnaires were only distributed at this site. This illustrated that there is still a great shortage of resources in South Africa, which is reflected in the fact that clinical trial personnel do not readily have access to the Internet or even to computers. A comparison of the percentages of responses received from the sites that were included in this trial is illustrated in Figure 1 below.

Clinical trial sites were chosen based on their accessibility to the investigator. They all are situated in or near to areas that were previously disadvantaged during the apartheid era. These areas are populated with members of low-income households and due to social, economic and infrastructure deficiencies are more likely to be impacted by the HIV epidemic. This, however, also means that the level of education among the participants in these trials is relatively low and this could be a contributing factor when it comes to their understanding of the importance of adherence to the study product.

This population group is however, a fair representation of the majority of the population in South Africa as these areas are densely populated and represent the

socio-economic situation of the vast majority of the South African public most affected by the HIV virus and its consequences.

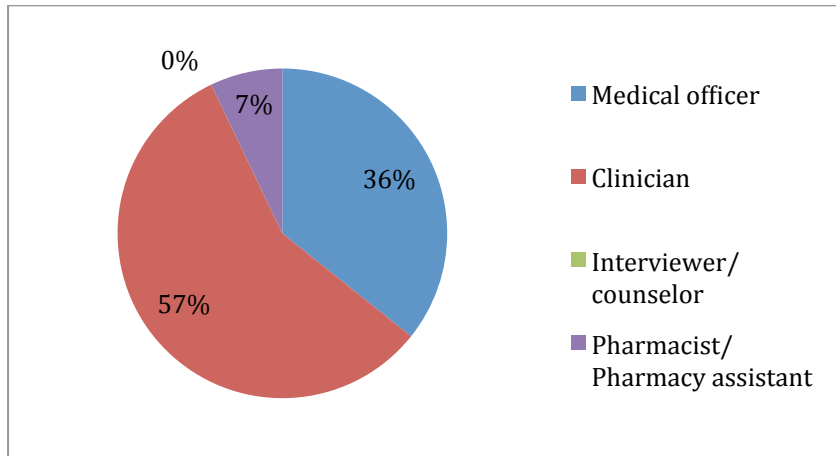


**FIGURE 1: PIE CHART REPRESENTING THE PERCENTAGES OF RESPONSES RECEIVED FROM THE CLINICAL TRIAL SITES AT THAT QUESTIONNAIRE WAS DISTRIBUTED**

**QUESTION 2 – IN WHAT CAPACITY DO YOU INTERACT WITH THE PARTICIPANTS?**

Clinical trial sites that participated in the trial were requested that all personnel working with participants of the HIV- related clinical trials, especially those on the adherence team should answer the questionnaire. An illustration of the ratios of the responses received is shown in Figure 2. The responses received thus consisted of 5 medical officers (36%), 8 clinicians (57%), 1 Pharmacist/Pharmacy assistant (7%) and 5 participants that completed the “other” category. These include: 2 nurses, 1 social scientist, 1 Principle investigator and 1 site investigator/project director. This shows that a wide variety of responses were received from many different fields in the investigating team.





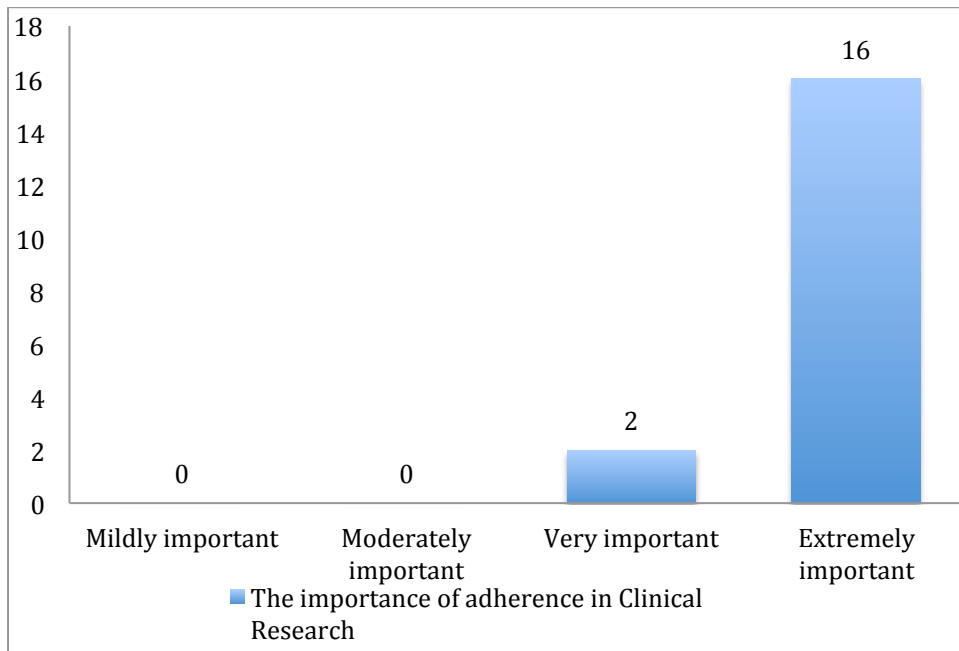
**FIGURE 2: PIE CHART ILLUSTRATING THE PERCENTAGES OF EACH HEALTHCARE WORKER SECTOR THAT RESPONDED TO THE QUESTIONNAIRE**

**QUESTION 3 - IN YOUR OPINION, HOW IMPORTANT IS THE ISSUE OF ADHERENCE OF SUBJECTS TO STUDY PRODUCT IN ORDER TO OBTAIN QUALITY RESEARCH?**

The participants in this study were asked their opinions on how important they thought the issue of adherence of clinical trial participants, to their treatment regimens was, to the outcome of quality research. Sixteen of the 18 responses stated that it was extremely important while 2 responses stated it was very important. No responses stated any perception below very important. This shows that research personnel have a good understanding of the impact that adherence and non-adherence has on the results obtained from clinical studies. The graphic representation of this result is shown in the bar graph below (Figure 3).

This is supported in the current literature where it is stated that the impact of adherence/non-adherence to the treatment regimen of a study product is extremely relevant such that it may dictate the success or failure of that particular study. (Bangsberg et al., 2000; Hogg et al., 2002; Paterson et al., 2000; Simoni et al., 2006).

Therefore it can be noted that study personnel are well informed of the importance of their co-operation in measures that are implemented to improve or maintain good adherence among study participants.



**FIGURE 3: BAR GRAPH SHOWING THE PERCEPTIONS OF HEALTHCARE WORKERS TO THE IMPORTANCE OF HIV MEDICATION ADHERENCE IN ACHIEVING GOOD RESEARCH.**

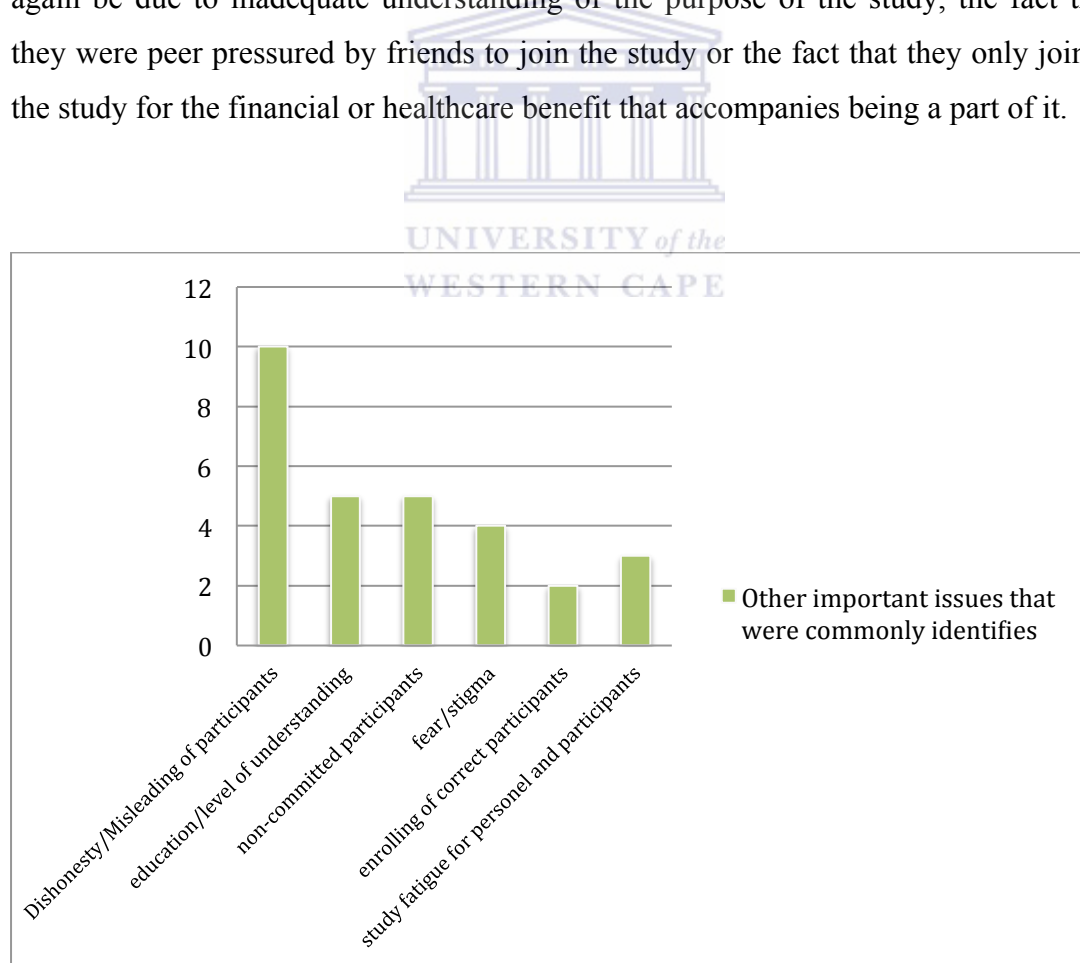
QUESTION 4 – PLEASE STATE ANY OTHER CHALLENGES THAT YOU THINK ARE SIGNIFICANT IN CLINICAL RESEARCH?

The survey also asked if there were any other issues, which the healthcare personnel thought are important and should be studied further. The response to this question produced some interesting new avenues for further discussion and research. In Figure 4, these responses are shown together with how common they were in terms of how many respondents expressed similar views.

The most common response (10 out of 18) states that dishonesty or misleading on the part of the participant as the most problematic issue that they face daily. This can be in terms of dishonesty about their reasons for joining the study, lying about the use of the product or even about their sexual habits. All these issues contribute eventually to low adherence and can adversely affect the outcome of the study. It has also been mentioned that participants may sometimes lie in order to keep the investigator or research team happy so that they do not lose favor with the researchers and lose out

on benefits such as the travel allowance or the healthcare that they receive at the clinic. Other reasons for lying could be peer pressure from friends in the study or those outside. This can also be linked to non-commitment to the study as they only joined because they are giving in to peer pressure.

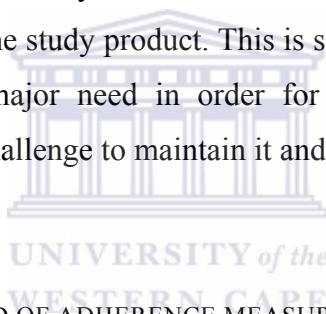
Lack of education or understanding on the participants' behalf is also considered a major issue as well as lack of commitment, with 5 responses claiming this. Lack of understanding could lead to participants using the intervention incorrectly or not using it at all. As South Africa is a developing country, education is an issue to be addressed. When recruiting participants it may also serve the researcher if the level of understanding of the participant is evaluated before enrolling participants that might not be able to comply with a complicated dosing regimen. Lack of commitment can again be due to inadequate understanding of the purpose of the study, the fact that they were peer pressured by friends to join the study or the fact that they only joined the study for the financial or healthcare benefit that accompanies being a part of it.



**FIGURE 4: BAR GRAPH SHOWING THE COMMON PERCEPTION AMONG HEALTHCARE WORKERS WITH REGARDS TO IMPORTANT FACTORS THAT IMPACT THE SUCCESS OF A CLINICAL TRIAL.**

Two respondents stated that enrolling of correct participants is essentially a major issue. This could be grouped in with education and commitment. Four respondents also noted that stigma and fear from threats originating from the community they live in is a major issue. This is an issue that has to be dealt with delicately as there are major implications for the health and safety of the participants in this regard. The best way to overcome these issues is to educate the community on the need and purpose of these studies as well as the ultimate benefit that they will be gaining from their involvement if these trials are successful.

When evaluating these responses, a trend can be noticed that most study personnel have identified issues that ultimately affect retention of participants in the study and adherence of participants to the study product. This is significant in that it can be seen that while adherence is a major need in order for good quality research to be produced, it can be a major challenge to maintain it and to improve it as well.



#### QUESTION 5 – WHAT METHOD OF ADHERENCE MEASUREMENT DO YOU USE DAILY IN HIV TREATMENT/PREVENTION CLINICAL TRIALS?

When questioned about the methods of adherence monitoring that are currently used by them, the cohort responded with many of the direct and indirect techniques that the literature prescribes (Chesney et al., 2000). These are shown in Figure 5 as received from this survey.

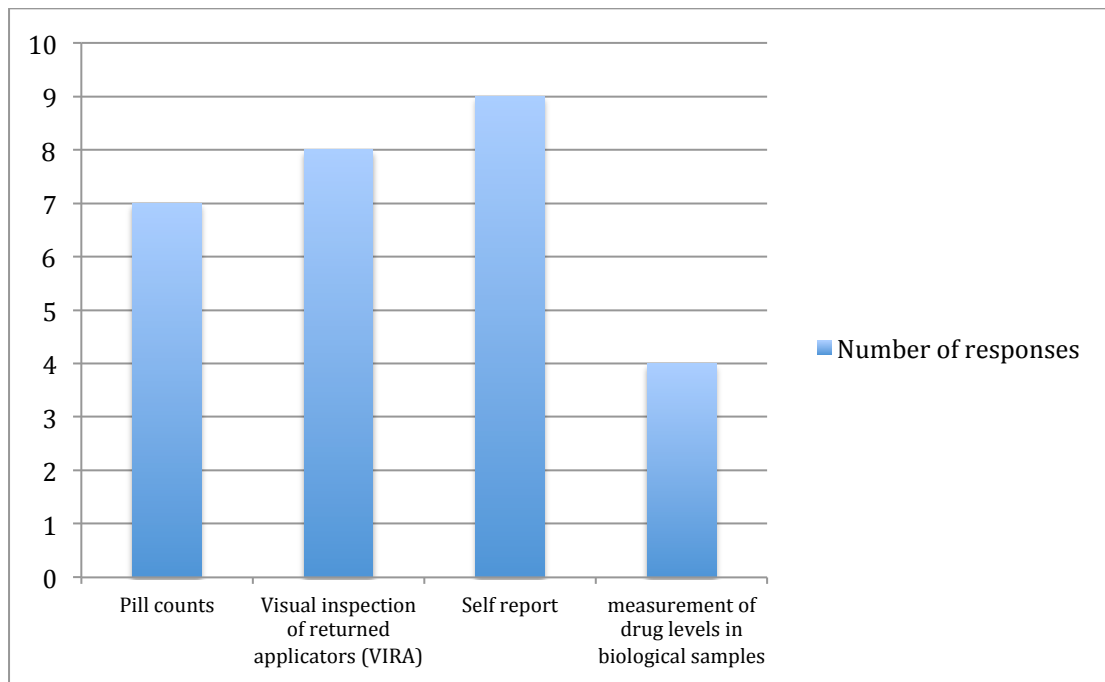
The most commonly used method for adherence monitoring as reported in the survey is the self-report measure (9 people). This is done either by individual completion of a medication diary or by interview conducted by motivational interviewers or social scientists. This tool has benefits as well as disadvantages. It is widely acknowledged in the literature as the most inexpensive and practical method to measure the product adherence (Walsh et al., 2002). Therefore the results received from this survey

supports the literature and shows that in practice self-report is indeed a widely preferred method of adherence monitoring.

Another method used is that of pill counts (7 responses) or Visual Inspection of Returned Applicators (VIRA) with 8 responses. The VIRA method is used in the case of a clinical trial studying the microbicide gel for intra-vaginal insertion (Tolley et al., 2010). These 2 tools fall into the same category of inspection of product to determine the adherence of the participant to the product instructions. This is a more objective method than self-report but can also be strenuous on personnel, as close examination of the returned product is required to calculate the adherence score.

Another notable measurement tool that was mentioned is the measurement of drug concentration in biological samples with 4 responses listing it as currently in use. This is an indirect method of adherence measurement but cannot be easily used in blind trials as unblinding can result. Thus this tool is normally used at the end of the study when maintaining of the blinding is no longer necessary. It is also a more costly tool, as specialized lab services are required to obtain the results of this measure.

Other tools mentioned in the survey include the recording of adherence on a barometer to demonstrate changing behavior of the participants and group discussions to evaluate the general acceptability of the product to the community.



**FIGURE 5: BAR GRAPH SHOWING THE MOST COMMONLY USED TOOLS FOR ADHERENCE MONITORING AS PER SURVEY RESPONSES.**

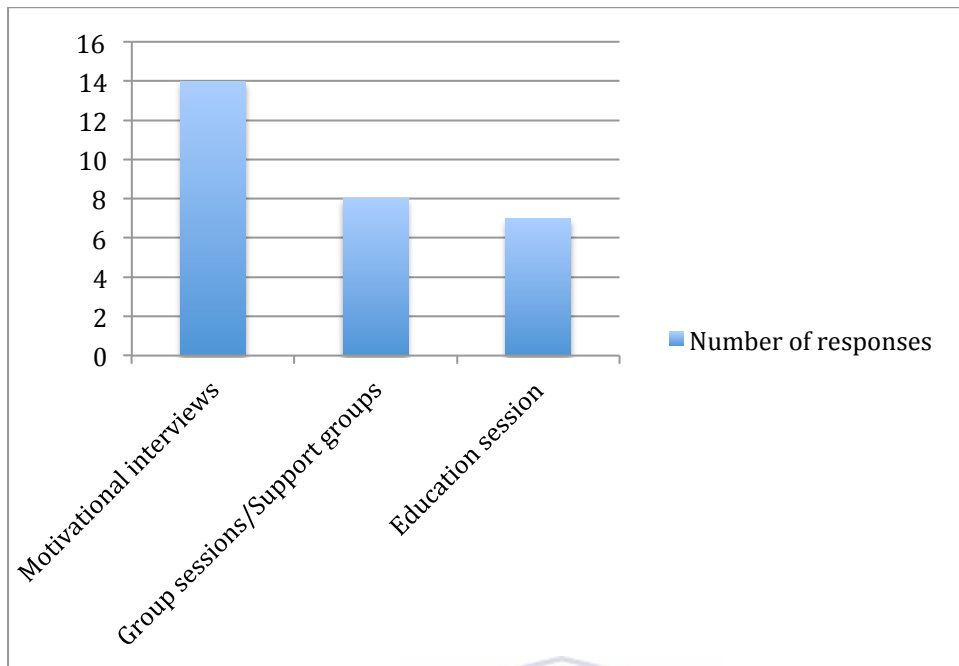


**QUESTION 6 – WHAT METHODS DO YOU CURRENTLY USE TO IMPROVE/ ENCOURAGE ADHERENCE?**

When questioned on the methods currently in use in order to improve or encourage adherence, the answers were varied and informative in terms of current popular practice. These responses are shown in Figure 6.

Almost all the respondents (14 out of 18) stated that motivational interviews are used as the primary method of adherence maintenance or improvement. Those responses that were counted in this number include those stating individual counseling as well as face-to-face discussions.

Group sessions and support groups were also stated as being used by 8 of the 18 respondents. These sessions include education sessions, foyer talks by various guests in the waiting room and group counseling sessions for participants that have problems they wish to discuss with each other or collectively address with clinical trial staff.



**FIGURE 6: BAR GRAPH SHOWING THE 3 MOST COMMON METHODS CURRENTLY IN USE IN ORDER TO ENCOURAGE ADHERENCE TO THE STUDY PRODUCT.**

Educational sessions were stated by 7 of the 18 respondents as a method that is currently being employed. This is carried out by educating the study cohort as they come on site as well as the community by sending study personnel to discuss HIV/AIDS related issues at community events and meetings. Also, posters and reading material are available on site to answer questions related to the trials as well as HIV/AIDS in general. Videos are also played in the waiting rooms to reinforce the education that is provided. These education sessions concentrate on the risks as well as steps that can be taken to prevent HIV infection. They benefit the community as well as study personnel.

Other methods currently being used include reminder SMS's, talks by various experts and religious/social leaders and appreciation tokens.

**QUESTION 7 AND 8 – WHICH OF THESE METHODS DO YOU THINK ARE MOST EFFECTIVE AND WHICH ARE LEAST EFFECTIVE?**

When responding to the questions asking the participant which methods they see as the most and which the least effective in encouraging adherence of participants, two main ideas were identified. This is illustrated in Figure 7.

These ideas are that participants in this survey feel that by far the most effective method used to increase adherence is the motivational interviews (9 Responses). This includes individual counseling on use of the product as well as one-on-one sessions discussing challenges that are faced in using the product. The second idea is that most healthcare workers do not feel that any method is without merit and that all efforts used to improve adherence are valuable. This is shown where 8 of the 18 respondents either did not answer the question asking them to identify the least effective method or answered this question with “none”.

However, 2 respondents noted that sometimes individual counseling sessions could be ineffective as they could be perceived by clinical trial participants as lecturing and thus tune out what is being said. It was also noted by two respondents that continuous education could also be ineffective as they are sometimes repetitive and begin to be ignored.

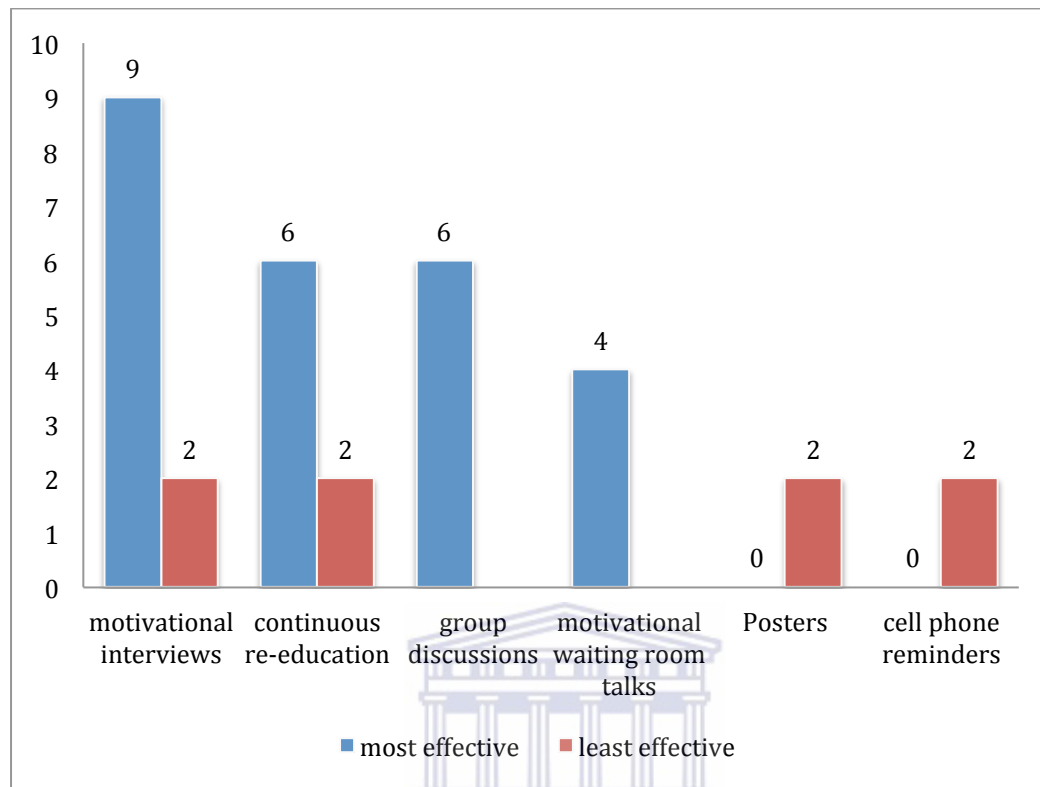
From the responses it can be noted that continuous re-education (6 responses), group discussions (6 responses) as well as motivational waiting room talks (4 Responses) were some of the most effective methods of improving and maintaining adherence.

This is encouraging as new methods that are being implemented involve increased educational programs as well as peer motivation and community support programs.

Among the tools that were felt to be ineffective were the posters (2 responses) and the cell phone reminders (2 responses). The posters were perceived as too unobtrusive



and boring. Therefore the likelihood of participants noticing them and taking an interest in the message conveyed via them was very low.



**FIGURE 7: BAR GRAPH COMPARING THE MOST EFFECTIVE METHODS OF IMPROVING ADHERENCE WITH THE LEAST AFFECTIVE METHODS AS PER SURVEY RESPONSES**

**QUESTION 9 – DESCRIBE ANY TRENDS YOU HAVE IDENTIFIED IN NON-ADHEREING SUBJECTS THAT COULD BE RELEVANT TO ADDRESSING THIS PROBLEM?**

Participants in this study were asked to identify any trends that they noticed in non-adhering participants that could be targeted in an adherence program (Figure 8). They identified various issues but 2 predominant ideas have arisen which seem to be prevalent. These are peer pressure (7 responses) and non-disclosure to the partner (4 responses).

Peer pressure is by far the greatest issue that influences adherence (41%). In fact many responses have detailed that peer pressure can originate from the home of the participant, the community that the participant is a part of or even the friends that the participant makes at the site. Some responses tell the story of participants that have

been in the trial for a long period and how they influence newer participants to “cheat the system” and mislead investigators and staff regarding their use of the products. They have learned the ways in which adherence is monitored and have developed means of misleading these tools so that adherence appears to be good when in actual fact the participants have not been using the product.

There are a few reasons for this, which have been identified. One of these reasons is that the community and the participants distrust the investigators and wish to only join the trial in order to benefit from the travel money or the healthcare they receive as a part of the trial. This is a problem that has been identified and discussed in the literature as participants in clinical trials are healthy and are sometimes not fully committed to the research in which they are an important component (Tolley et al., 2010). Another reason is that participants feel that they are on the placebo and think that it would not make any difference to the outcome if they use the product or not.

Non-adherence is also as a result of the stigma attached with using any intervention for HIV prevention. Participants feel that their partners will think that they are HIV positive if they see tablets in their homes or that they are trying to give them HIV when they insert the gel before sexual intercourse as per instructions.

The next issue identifies is that of non-disclosure to partners (24%). This is an important issue, as it seems that participants fear the repercussions of disclosing to their partners that they are a part of clinical trial or that they are using a measure to prevent the transmission of HIV. Partners of the participants sometimes feel that it is a sign that their partner is promiscuous or cheating on them particularly in trials conducted with predominantly female participants. Some are mistrustful and feel that using an intervention causes HIV to be transmitted more easily, while others feel that it is unnecessary and that they do not have a need to use such a method. This sometimes forces the participant to leave the trial when their partners find out. Sometimes they remain in the trial but mislead the investigators regarding their use of the product, as they are afraid to admit the reason why they are not adhering. Their

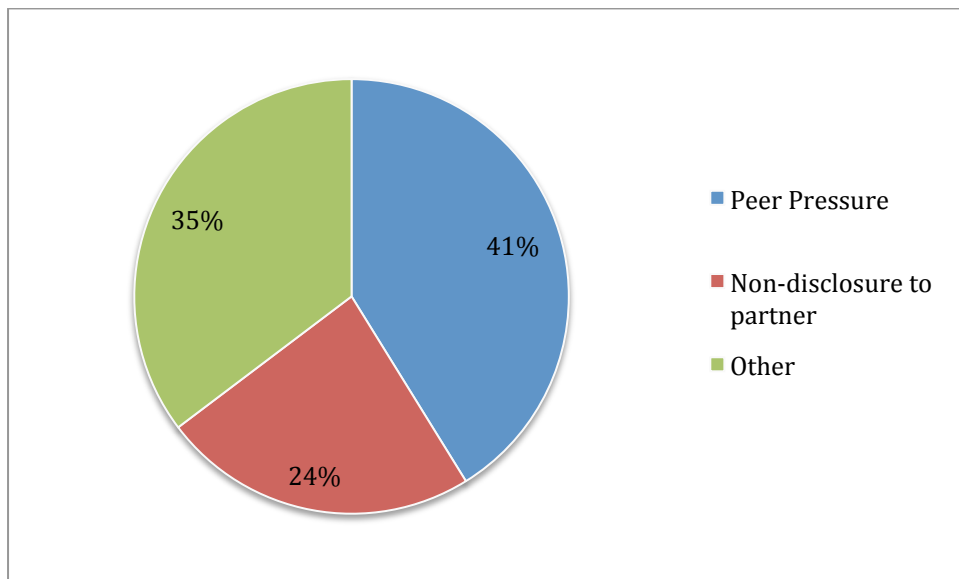
participation in the research endangers them to domestic violence or retaliation from the community. These are all issues that can be addressed by more community involvement on the part of the investigators as well as educating the community on HIV, and its risks and importance of research.

The remaining 35% (6 responses) had a variety of ideas and trends that they felt were contributors. A single response stated that clinical research staff should make more of an effort to determine the root cause of non-adherence in each situation and that enough was not being done to reassure the participants and ensure that they are fully committed and understand the research and the importance of their honesty and involvement. Two responses identified that recruiting the right participant at the start of the trial is a key issue. Some participants join the trials with no real commitment and this impacts their willingness and determination to follow a dosing regime as set out to them. Participants, which are only willing to join the trial for a monetary or health services benefit should also be identified and not be enrolled. Some participants also begin the trial with a commitment, but as time goes by this commitment wanes and their priorities wane resulting in them not being as serious about it as they used to be. This issue can be addressed by re-education and reminders to the participant of the importance of their co-operation.

Other issues also include the inconvenience of a complicated dosing regimen, which can be difficult to remember and incorporate into their daily routines. Also, when the participants experience undesirable adverse effects they become less likely to use the product. This issue has been identified frequently as the primary reason for non-adherence in patients on HAART treatment regimens (Gary et al., 2013; Lenzi et al., 2013) and remains one of the most important issues to overcome when planning an adherence intervention strategy.

Participants do not feel that the protection that may be afforded to them by the use of the product is sufficient to overcome the adverse effects. Furthermore, in double-blind placebo controlled trials many participants feel that they are on the placebo if they

have no adverse events and then begin to skip doses and become non-adherers due to this perception.



**FIGURE 8: PIE CHART SHOWING THE PROPORTIONS OF PARTICIPANTS IN THIS SURVEY THAT HAS IDENTIFIED THE ABOVE TRENDS IN NON-ADHERENCE**

QUESTION 10 – PLEASE DESCRIBE ANY STRATEGY FOR IMPROVING ADHERENCE THAT YOU FEEL SHOULD BE IMPLEMENTED TO ADDRESS THIS PROBLEM.

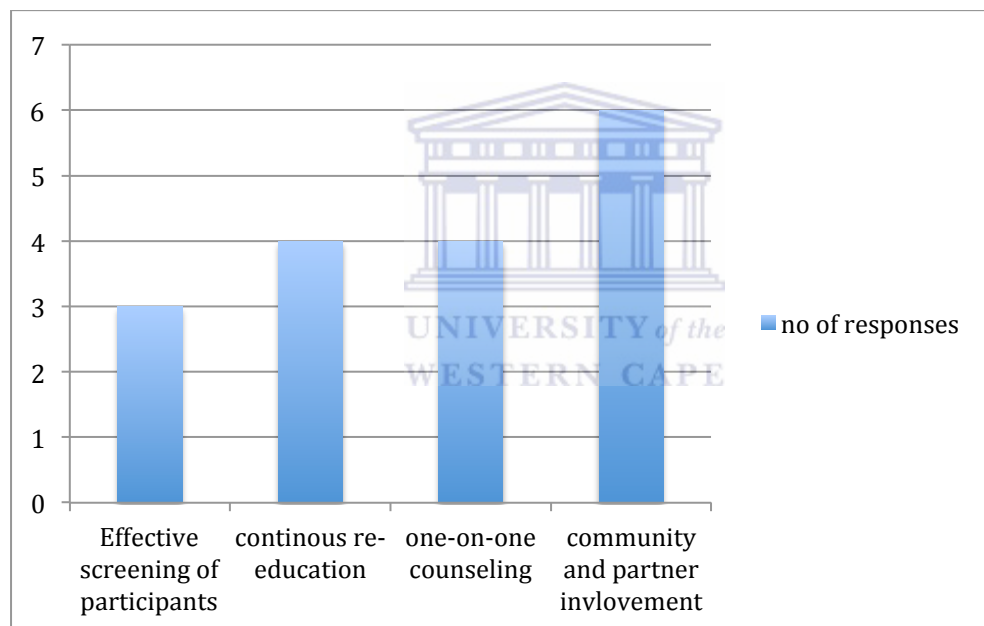


The final question that was asked in the survey was for respondents to suggest any strategies or ideas that each felt was important to be implemented in current clinical trials or to be considered in the future. The results for this are shown in Figure 9.

The most prominent idea that was suggested by 6 of the 18 respondents is that community and partner involvement needs to be increased. The clinical trial site should be active in the community in terms of providing education on the trials that they are conducting and should take the time to address issues that come to them from the community. They should take an interest in how the trial affects the community as a whole and also gain support from the religious leaders to provide a good support system for the participants. The partners of the research participants should also be more involved in the process and should be accommodated with regards to questions they have and concerns. This is also important as the partner of the participant can be

brought into the trial as a support system in order to encourage the participants to use the product according to the instructions. If a positive and respectful attitude is cultivated towards the research staff then there will be less room for misunderstandings and suspicion and more trust will be placed in the product when it is marketed if the myths and conspiracy theories can be dealt with in the trial stages.

Out of the 18 responses received, 4 stated continuous education and one-on-one counseling as areas to concentrate on. These 2 areas are currently heavily used in clinical trials as self-report is a widely used method of adherence measurement.



**FIGURE 9: BAR GRAPH SHOWING THE NUMBER OF RESPONES FROM THIS SURVEY THAT EXPRESSES COMMON IDEAS REGARDING PLANS FOR IMPROVING ADHERENCE OF PARTICIPNATS IN CLINICAL TRIALS**

Re-education is also widely used and has been identified as a way to improve adherence in patients that are on HAART treatment regimens (Holzemer et al., 2000). Re-education is of utmost importance as participants may loose interest in the study after some time and their commitment to the study needs to be reasserted often. This means they need to be reminded of the important role that they play in the research

process as well as the benefits to the community and to themselves that will be available upon the success of the trial.

One-on-one counseling or motivational interviews are also recommended by researchers in order to help participants overcome their psychological barriers to the use of the product (Olem et al., 2013). This is a method that can easily and inexpensively be used while self-report is being conducted. This also shows the participants that the study is not only to gather data but also can benefit them in their lives.

Three out of the 18 responses stated that effective screening of participants is an aspect to consider. This is a major issue and something to consider as good participants with commitment to the research make a clinical trial much easier for the researchers. Screening especially should be conducted in such a way as to pin point potentially problematic participants before they are enrolled. Participants that move frequently and do not have stable addresses are at risk of defaulting and sometimes are unable to be traced. Others that are not committed or do not adequately understand the aims of the research are more likely to be non-adherent or drop out. These are factors, which could detrimentally affect the research results if not taken into consideration.

It is also stated in the literature and shown in the above results of the survey that while self-report can be an opportunity for participants to mislead investigators, it may also provide the investigator an opportunity to influence the adherence of the participant as well as identify trends in non-adherence (Simoni et al., 2006). The interview that is conducted in order to gain this information can be simultaneously used to pass the message of adherence on to the participant. This interaction between the participant and interviewer can also be used to determine the group perception of the study and the root causes of non-adherence.



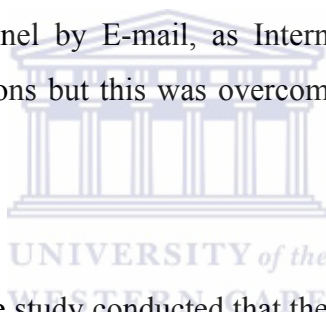
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## CHAPTER 6

### CONCLUSION AND RECOMMENDATIONS

This study was undertaken to gain an understanding of the perception that prevail among clinical research personnel regarding the importance of participant adherence to dosing instruction and their ideas for intervention strategies to improve this adherence.

One of the challenges that were faced in conducting this research is in reaching the target group and acquiring the required information from them. Difficulties arose in reaching the research personnel by E-mail, as Internet connectivity is not widely available in some of the regions but this was overcome by providing hard copies of the survey wherever possible.



It can clearly be seen from the study conducted that the perception among researchers working in clinical research regarding HIV related clinical trials is that adherence is a major issue. It can also be seen that there are many factors, which affect the adherence of participants to the product, and these have to be dealt with in a sensitive manner by the research team. Other issues that were identified are participant retention and lack of commitment on the part of the study subjects.

In this study it has been established that adherence measurement done using self-report is a very cost-effective tool that is easy to use and acceptable to the healthcare workers that are involved in the clinical research. It is also a good tool to use in any adherence intervention strategy as most of the one-on-one counseling can be done while staff are interviewing for, or assisting the participant to complete, the self-report questionnaire.



From this study it can also be seen that one of the biggest challenges that research personnel face when conducting a clinical trial is to overcome peer pressure. This is in the form of participants influencing each other to not use the product and teaching them ways to avoid detection of this behavior. It can also come in the form of pressure from society and the community if the community is averse or suspicious of the trial and its motives. This is a major problem as it can result in violence against participants or research staff and can jeopardize the research if not handled timeously and delicately.

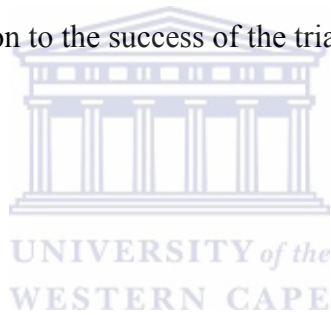
Further research and discussion is needed in order to develop better strategies to deal with issues such as education, stigma and a lack of commitment on the part of the participants.

When planning a clinical trial in a certain area, it would benefit the researchers to first ensure that the community will welcome such a development and to gain the trust of the community in addition to complying with Good Clinical Practice (GCP) guidelines. Bringing education and awareness will add to the community's acceptance of the research and garnering support from the society will be beneficial in the retention of participants. It is also important that when initiating clinical research in an area, something must be given back to the community in terms of HIV awareness and a relationship that allows for the community to express their problems must be established.

As pharmaceutical companies begin to bring more and more HIV pre-exposure prophylaxis measures to clinical trials, it is important that they consider some of the points that have been discussed in this study. As this study is based on the current prevailing opinions among the participants that are generally enrolled in these trials and the experiences of the research staff that work directly with these participants, the information that this study provides could make it easier for an innovator company to plan their clinical trial.

An important issue that can be taken away from this study is that cultural and educational considerations should be paramount. Ignorance on the part of the community can breed enmity and suspicion. Therefore educating the community and being culturally sensitive in the approach that is used to enroll participants is very important for the success of the trial.

Finally, during screening and recruitment of participants, a part of the recruiting strategy should be to ensure that participants are aware of the importance of their commitment to the research and that their reasons for joining the trial are not influenced solely by the financial benefits. Participants should be carefully screened in order to ensure that they understand the importance of the research as well as the importance of their cooperation to the success of the trial.



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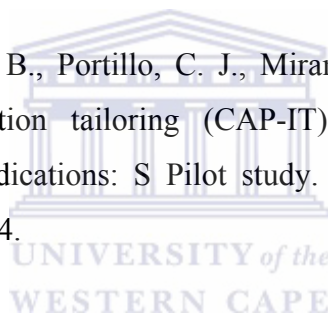
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# APPENDICES

## APPENDIX I: SAMPLE OF SURVEY SENT OUT TO PARTICIPANTS

[SURVEY PREVIEW MODE] Adherence as an issue in clinical trials Survey

2014/05/11 10:57 PM

### Adherence as an issue in clinical trials

**1. Please note that this questionnaire is for research purposes. The answers the you provide will remain confidential.**

Name:

Company:

Address 1:

Address 2:

City/Town:

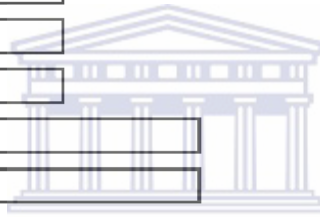
State/Province:

ZIP/Postal Code:

Country:

Email Address:

Phone Number:



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**2. In what capacity do you interact with research subjects?**

Medical officer

Clinician

Interviewer/counselor

Pharmacist/Pharmacy assistant

Other (please specify)

**3. In your opinion, how important is the issue of adherence of subjects to study product in order to obtain quality research?**

Mildly important

Moderately important

Very important

Extremely important

**4. Please state any other other challenges that you think are significant in clinical research.**

**5. What method of adherence measurement do you use daily in an HIV treatment/prevention clinical trial?**

**6. What methods do you currently use to improve/encourage adherence?**



**7. Which of these methods do you think are the most effective?**



**8. Which of these methods do you think are the least effective?**

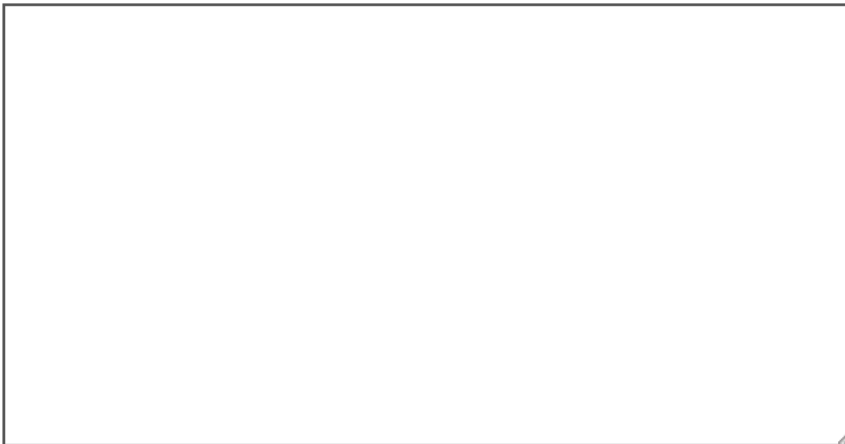


**9. Please describe any trends that you have identified in non-adhering subjects that could be relevant to addressing this problem**



The image shows a watermark of the University of the Western Cape logo, which consists of a classical building facade with columns and a pediment, with the text "UNIVERSITY of the WESTERN CAPE" below it.

**10. Please describe any strategy for improving adherence that you feel should be implemented to address this problem**



Done

Powered by **SurveyMonkey**  
Check out our [sample surveys](#) and create your own now!

