A REVIEW OF RECRUITMENT STRATEGIES WITHIN THE CLINICAL INFECTIOUS DISEASES RESEARCH INITIATIVE (CIDRI) GROUP FROM 2007-2013, 4 STUDIES

René Goliath

This thesis is submitted in fulfilment of the academic requirements

for the degree, of

Master of Philosophy in Clinical Research Administration

in the Faculty of Health Sciences

University of Cape Town

August 2018

As the candidate's supervisor, I have approved this dissertation for submission.

Name: Dr Widaad Zemanay

Signed: Signed by candidate

Date: _30 August 2018 ____

Declaration

I hereby declare that: (1) the above thesis is my own unaided work, both in conception and execution, and that apart from the normal guidance of my supervisor, I have received no assistance apart from that stated below; (2) except as stated below, neither the substance or any part of the thesis has been submitted in the past, or is being, or is to be submitted for a degree in the University or any other University. I am now presenting the thesis for examination for the Degree of Master Philosophy in Clinical research administration

Signature: Signed by candidate

Name: René Goliath Date: 30 August 2018

Abstract

The Clinical Infectious Diseases Research Group [CIDRI] has conducted high impact research over the last decade in Cape Town specifically in the townships of Khayelitsha and Mannenberg. None of this research would have been possible without robust strategies to recruit and retain study participants. Four different completed studies [1] with different study designs have been selected, which will show the different approaches to participant recruitment into clinical research. This review will evaluate this process in relation to the approved protocol recruitment strategy, the amendments, which were required for modifications, the ability to retain participants to the end and the composition of staff used to achieve study outcomes. This entire process has been recognised as a necessary research skill and the term recruitmentology Epstein [2] has become a practice pivotal to the research process.

Recruitmentology Epstein [2] has been unpacked to illustrate how minorities have been recruited, overlooked and over researched in the United States (US), and that experience has given a new perspective to the processes involved. Although in the South African context we do not have the identical issues to the US, these ideas can be translated in our circumstances, as both research populations can be considered as marginalised. We are challenged in the township of Khayelitsha with service disparities, which are generally impacted by the presence of clinical research groups. Although Khayelitsha [3] has three large Day Hospital facilities, a newly built 150 bedded secondary level hospital and 11 local clinics, offering a consistently high standard of care; it remains a challenge.

The CIDRI group partnered with the health services, supporting them with extra staff in the way of nurses, doctors and clinical research workers, while in return benefiting from the health system by being able to conduct effective studies. This has been and continues to be a mutually

beneficial relationship, as CIDRI has been supportive to health services and the service has been a research partner of many research protocols including one of the studies being reviewed.

Through the process of reviewing the databases of these four different CIRDI studies, we can examine the successes, challenges and a possible model of recruitment in the township of Khayelitsha. These studies have been chosen as they have been successfully completed by CIDRI and the databases have been locked. Each study has a different study design, from a pragmatic randomised control study, a cross sectional study, a seasonal follow-up and longitudinal study. Close attention will be paid to proposed recruitment strategy as per approved protocols, amendments (which impacted the recruitment process), staff structure, time frames of recruitment, retention and impact on study outcomes.

This review will attempt to answer the following:

1. Was the proposed recruitment strategy followed as per study design and approved study protocol?
2. Was the overall recruitment impacted by staffing structure and allocated recruitment time frames?
3. How were study outcomes impacted by recruitment and retention?
4. Tuberculosis/Human Immuno-deficiency Virus TB/HIV were the diseases of study in all four studies, do these two diseases have specific challenges which impact recruitment and retention?

Acknowledgements

I owe my gratitude to all those who have supported me during my course work and the writing up of my thesis.

I am firstly thankful to all the volunteers who enrolled in the clinical studies reviewed in this thesis, the lead investigators, research staff who worked on the studies and to Professor RJ Wilkinson who allowed me access to these databases.

My deepest gratitude to my supervisor; Dr. Widaad Zemanay who continued to support and guide me during difficult personal circumstances. Her support and guidance helped me overcome many anxious times and self-doubt as I worked towards completing this thesis. I am grateful for her encouragement and practical advice and helping me understand and enriching my ideas.

I am also thankful for my colleagues and friends who offered me support. Andrea DeLuca, the first person to read my thesis when it was still just a mass of words. Her encouraging responses gave me the courage to pass my work on to others and accept all the constructive criticism. Thanks also the Dr. Leizel Swartz who painstakingly taught me formatting when the page numbers and the insertion of tables pushed me to the edge.

To my aunty, Jane for carefully reading and commenting on this this manuscript, gently correcting my grammar with kind notations in the margins.

Most importantly, none of this would have been possible without the love and patience of my family. My mother who regularly enquired about progress I was making, my immediate family who have been a constant source of love, concern, support and strength during this long process. I would like to express my heart-felt gratitude to my family who encouraged me throughout this endeavor. Lastly thank you to my friends who are very grateful this process is now complete.Glossary

CIDRI	Clinical Infectious Diseases Research Initiative
Pragmatic Trial	Trial designed to test the effectiveness of the intervention in a broad routine clinical practice.
Cross sectional Study	An observation and data collection of a single point in time
Longitudinal Study	Several observations of the same subjects over a period of time
Seasonal Follow-up	The construct of seasonality, observation the same subjects from one season to the next

25(OH) D levels	25-hydroxy vitamin D blood test, a test for Vitamin D levels
ARV's	Anti- retrovirals
BATNA	Best Alternative to A Negotiated Agreement
CAB	Community Advisory Boards
CRW	Clinical Research worker
DAT	Data Abstraction Tool
DoH	Declaration of Helsinki
NGO	Non-profit Groups and Organizations
GCP	Good Clinical Practice
HIV	Human Immune Deficiency Virus
IPT	Isoniazid preventative treatment for TB
ICH	International Code of Harmonization
IFC	Informed Consent
KY	Khayelitsha
MMPs	Matrix metalloproteinases
MSF	Médecins Sans Frontières, or Doctors Without Borders
NKTs	Natural killer T (NKT) cells
TB	Tuberculosis
US	United States

Table of contents

1 Background

The ability to recruit is the essence of any research project, for without participants volunteering to join the projects, no research would be possible. The ability to effectively recruit requires the skilled art of conversation. In this art of conversation, the researcher engages the potential participant in learning about the risks and benefits of volunteering, and if these talks fail and no agreement can be reached in the context of clinical research, this failure would prevent enrolment.

In the case of clinical research the recruiter must understand both sides of the situation; that of the volunteer and the requirements of the research project. The potential participant also needs to feel heard by the recruiter in-order to listen. This is especially true when you are talking about informed consent. The research volunteer should be empowered to understand the project, and should also feel powerful enough to say no. The researcher must be cognisant of the power relationship held by healthcare workers and constantly seek not to become a more powerful role player in the recruitment process.

In-order to work through the power process, the study team member doing the recruitment must one; know the protocol extremely well, two; to be able to clearly describe the study and three; be able to engage in an informed discussion. Feedback to the team and a review of the recruiters' performance is essential, for example by always asking: how can we do better or differently? All study team members should be prepared to demonstrate understanding of the situation, in the area and healthcare practices and attitudes. They must also adapt approaches for specific situations, by acknowledging differences of belief and custom, avoiding stereotyping, and focusing on each person is an individual, as this directly impacts recruitment and retention.

Recruiters are “people first” with values, backgrounds and viewpoints. Whether they would they take part in this research; is important. This can be the most important ethical principle that recruiters can use as a moral compass. This process will result in a two-way relationship. Healthcare is emotive by nature; this can sometimes contrast with the motivations of the study investigators who are not directly connected to participants, and can be motivated by enrolment figures and publications.

Roger Fisher and William Ury[4] believes the most powerful interests/motivators are basic human needs. The volunteer needs to feel secure. Mutual gain and protection; is vital, and the recruiter needs to identify shared interests, and develop a Best Alternative Negotiated Agreement (BANTA). Issues of trust, length and type of consultations, convenient times of clinic, all study activities and the rights of the participants to be clarified in the discussion with the potential volunteers by the recruiters.

Project leaders need to start slowly with a small target. They also should make an investment in staff and allot the time and resources and prepare for the recruitment process. As a team, you need to realize your power and acknowledge it. There is power in developing a good working relationship within the group; there is power in understanding the other viewpoint which is helpful when recruiters are from the community and therefore a community advocate. Understanding this power can help the participant to see the benefit of participation, and after thorough study consent gives permission and is enrolled.

The ultimate goal of recruitment is enrolment, as well as establishing trust and increasing motivation. Tappen [5] suggests a plan(10 steps) that recruiters could follow to be effective and for completing participant recruitment and enrolment.

- Specify those needed for the study; know your inclusion and exclusion criteria.
- Develop recruitment plan. Which population do you need to access, potential barriers to participation ?
- Know who to contact, meet the community contacts you may need support from the Community Advisory Board (CAB)
- Disseminate information via systems which are appropriate to the community, flyers, radio, community newspaper and Non- Governmental Organizations (NGOs)
- Ask or invite people to join by mass community information systems
- Good Clinical Practices (GCP), protocol training and protocol consent training, must be current and well understood
- Screening, could be done before consent by way of information sharing and asking only those eligible to attend.
- Enrol as per protocol
- Retain by establishing a good relationship
- Report back to community via CAB

These ten steps are closely linked to the fundamentals of recruitment. Participant recruitment is both an art and a science; [2]Epstein 2008 calls the emerging area of applied research; recruitmentology. It includes all disciplines such as psychology, nursing, sociology, anthropology, marketing, and public relations. Epstein[2] refers to recruitment as an emerging applied science, and not merely a chore to achieve the protocol. He does, however, consider that this process is prompted by clinical researchers needing to achieve targets. Recruiters need to be

knowledgeable about sociocultural properties of the community. The term recruitmentology has evolved due to the increased pressure to recruit participants resulting in the development and documentation of the methods used. Recruitmentology practitioners who are the study team members must be able to produce and disseminate knowledge about successful recruitment and retention of participants. Particularly understanding the “hard-to-recruit” populations, which is a term used by Epstein, this group could be better described as challenging groups communities who are impacted by protocol requirements. They may require repeated visits in longitudinal studies, or long study visits with many procedures. Also, groups who are resistant to research struggle with acceptance of their disease and are challenged by follow-up, especially if they have recently gained employment when the level of unemployment is generally high. Recruitmentology evaluates the efficacy of techniques required to get people to join research trials, “getting them to yes.”[4], which we describe as the group who voluntarily joins the study. Effectiveness of recruitment depends on the collective memories of the community being recruited, in the case of Epstein,[2] it was racism and research abuse. Effective recruiting results in a good collective community memory and the volunteers will share their good experiences with others in the community. His paper focuses on the trust recruitmentologist devise and includes new models of participatory research. He also looks at the impact at which globalism intensifies the issues around recruitment and retention with the heightening risks of exploitation of the racialized global underclass. Also discussed are underrepresented sub-populations, evaluated by gender, race and disease. Retention into longitudinal research projects and clinical trials not only require a good first impression on the research subjects but the hard work of maintaining the long-term relationship. This relationship starts with the practical challenge of finding the appropriate individuals to participate in clinical research while being cognisant of the inclusion and exclusion criteria and the diversity of the cohort. With the correct sampling scheme, recruiters should not have to be concerned about ensuring that the cohorts/study groups are balanced.

Epstein [2} reminds researchers they have to be marketers of their research, which is costly and may demand extra staffing time, which must be budgeted for. Even when staff are correctly budgeted if they are not effective marketers of the research the recruitment will fail. Recruitment efforts have to be community specific using the allocated budget on activities which are effective in that community.

Delays in recruitment adversely affect the budget, for example, staff allocated in budget for 12 months not 18. Epstein [2] notes that more than 50% of trials run a month or more late because of poor recruitment. This could be seen as a business opportunity where recruitment is “turned over” to drug companies and research recruitment companies to achieve targets. This is a steadily growing service. Epstein [2] states that during the period 1992-2001 study participants recruited by companies grew from 7-20 million. All these companies would have to be GCP compliant and closely monitored to ensure participant safety and protection. All recruitment efforts would be naught if not very closely linked with retention of those participants, which is not an evident role “companies” play according to Epstein [2]. Followed by recruitment is the vital process of retention Aron Shapiro, [6] makes a good argument for robust retention processes.

Aron Shapiro, [6] in the discussion around retention of study participants in the trial, argues that the inability to retain participants leads to increased trial costs, longer trial duration, less statistical power, all of which could impact the validity of results and contribute in low staff morale. Shapiro [6] also highlights the reason for participants joining a study as a way to access potential treatment as some the diseases have limited options for care; or if the service does not have the capacity to effectively treat the disease. Retention is linked to the initial contact made with the participant, what is shared at that contact, what information is collected and what the study offers must be what that the participant has hoped for. Ideally the participant should not be only concerned about

details of the study, but rather be aware of what the research aim is and how they fit into the study achieving the outcome.

The trial staff must also understand the movements of the participants. Shapiro[6] uses the example of the study being done when the disease is more prevalent among the aged who may move to warmer climates in the summer. If the study investigators are unaware of factors such as these they will be lost to follow up. Informed consent is the most critical document for recruitment and retention and must be used throughout the trial; which would reduce dropout rates and protect the participant throughout the trial. Consideration around transport needs to be made when recruiting, as this will also impact on the ability of participants to attend follow-up visits. Aron Shaprio,[6] also emphasizes the need to respond to issues the participants discuss at their follow-up visits which may include, frequency of visits, attitude and empathy of staff. Systematically working through these issues, as they arise, can decrease the dropout rate. The use of technology is a valuable tool when encouraging participants to attend if the participants have access to this technology; sending reminders to cellular phones and even sending emails can be explored. Volunteers are given an option to leave the study at any time, therefore the study team must avoid poor appointment scheduling times and long waiting periods. Good knowledge of window periods allowed for each visit, a comfortable waiting room and proportional transport re-imbursements are essential parts of this process. Recruitment and retention cannot happen if we don't have a good understanding of the community, and over estimation of the availability of volunteers is a common error, as shown by Autumn Dawn Galbreath, *et al* [7].

In the study by Autumn Dawn Galbreath, *et al* [7] when carrying out 2 large single-centre randomized, controlled clinical trials was firstly that researches over estimate the number of qualified willing participants. They write about the recruitment process and comparative success of various recruitment strategies, their study teams travelled to clinics and enrolled 1971 participants from a total of 54 385 identified potential participants; the question could be asked if

the strategy being used was the correct one. This study used 6 recruitment strategies and evaluated their staffing requirements, the number of potential enrolees, total enrolment, cost to enrolee, retention rate, the cost to the completer and total cost to the study. It is the opinion that these are excellent strategies to use to evaluate the impact of the study on participants and study team and cost effectiveness of recruitment and retention. Print and broadcasting media interviews resulted in the best retention, and they were also the most cost-effective. Participants were invited for interviews at no cost to the study team, and the only cost they incurred were incentives paid to the participants when they attended the study visits. In the next study though they used paid print, radio and television media to inform the community of the study which was a costly exercise, but the retention rate was 30%, which was less than the free media interviews used on the first study, showing that every community responds in a different way. This study also has 2 diseases of interest and this may also have impacted on the community's response to recruitment and retention. It is noted that "marketing strategies" are helpful in planning future trial recruitment and budgets; it would also be beneficial if they were included in protocols.

Budgets for recruitment cannot only focus on strategies, but time lines for recruitment, staff cost and impact on scientific integrity must also be considered. Lisa K. Berger, *et al*[8]; discusses the scientific integrity and cost-effective strategies when recruiting participants for intervention research. They believe that the participant recruitment process determines the soundness of the study sample and the quality of the intervention is highly dependent on the participation of an adequate and representative sample. They propose systematic approaches for participant recruitment to ensure a sound sample, which should be phased in over a period of time. Phase 1 would be generating initial contacts by employing study team activities to solicit potential participants; phase 2 is the consenting process with full disclosure of risks and benefits; phase 3 would be screening to determine whether or not potential participants are eligible for study participation and phase 4 is enrolment and retention, randomization of eligible participants and

retaining them in the study. This is sometimes attempted simultaneously which results in the phases being ineffective. Strategies for each phase must be well planned and evaluated for effectiveness throughout the process.

Phase 1: generating initial contacts, the community awareness is raised to avoid suspicions about potential risks of intervention research. Trust must be built and research teams must know their local community. Trust is also enhanced; when previous studies were sensitive to the community structures as word of mouth advertising is very effective. Caution to be exercised during disease research in order to avoid stigmatization and confusion. Recruitment flyers are to be carefully worded. Other methods of making contact include mass media and formal relationships with other local health care facilities and NGO's working in the community.

Phase 2; consenting with full disclosure of risks and benefits, determines the degree of success in ethically recruiting and retaining participants. Issues like understanding "placebo", invasive investigations and "random assignment", are fully explained. Staff actively practicing protection of human subjects is not negotiable and all consents should include the 3 vital elements of information, comprehension and voluntariness. Consents should be written and presented at an educational, language and culturally acceptable format. Employing consent procedures that enhance the consent process is valuable. First part of the appointment is devoted fully to the consent, opportunities for questions, answers and private reading are given. Staff to be trained to do consents and to share study information in a standardized way. Other options are rolling consent procedures. This involves that thestaff go through consent page by page and each page is discussed and initialled. Intermittent informed consent interviews can take place throughout the study period where key points are emphasized. This model encourages active and continuous involvement by participants in the decision-making process about study participation. Regular reminding participants of pending study procedures that were only mentioned in the initial consenting process, is absolutely vital when doing longitudinal studies.

Phase 3; screening, gives the study team time to fully apply the inclusion and exclusion criteria. The participant must fully understand why they are ineligible for the study, it must be explained in a very explicit way; that they are able to explain to others in simple language the criteria for being included or excluded from the study, for example “if I’m excluded today it is because I have symptoms of tuberculosis. I may be screened later after my tuberculosis work-up is complete and is negative.” Participants also need to be informed of the opportunity to repeat their screening if they are not eligible on the day due to a short-term issue; e.g. completion of a course of antibiotics. High dropout rates could be attributed to inadequate screening and participants who are not motivated to participate. Study staff may also consider excluding participants at this phase who have incomplete or unreliable demographic data, which will impact follow-up. Berger, L.K *et.al* [8] also considers the cost effectiveness during this screening step and may institute pre-screening as required, for example, such as prevention and wasting expensive processes of large recruitment teams when some of the screening can be done by a few staff members telephonically. The screening activity gives the team an opportunity to build a good rapport with the participants and this initial contact; helps to establish the trust, which will impact the retention.

Phase 4; enrolment and retention, when doing intervention studies, which include populations who are vulnerable, extraordinary efforts need to be developed to enrol and retain a sufficient diverse sample. It is important that partnerships are formed with the stakeholders in the community such as, community based organisations with the purpose of and developing trusting respectful relationships. Employing retention efforts must be tailored to the needs of the study participants. Investigators need assistance from the community to keep the control group uncontaminated by ensuring that the community is aware of the study intervention. Studies could also develop participant “roles and responsibilities” which describe study obligations and expectations throughout the study. Study staff should also seek to minimize the lag time between

the first contact with the participant and enrolment; as this would reduce attrition due to loss of interest or frustration. Once enrolled, visit times and staff attitudes and clinic planning impact retention, as does the availability of the staff to answer participant's questions. While incentive payments are fraught with ethical issues and they do impact the retention of participants. The amount paid should not be coercive, but be related to the nature of the research activity. Participant protection throughout these four phases is vital.

Participation protection is the cornerstone of all clinical research and at no time should the participant feel coerced. The International Code of Harmonization (ICH) guidelines 2012 ;[9] Declaration of Helsinki (DoH) is the official guideline by which all clinical trials must operate in order to protect human subjects involved in the studies. All staff must be GCP trained; lead investigators must ensure that all staff are appropriately academically qualified for their specific role. This guideline covers ethical permission, protocol training, and recruitment. It covers all-important aspects of conducting research starting with informed consent, confidentiality, data collection, case report forms completion, audits, and roles of study staff, GCP, ethics committees and institutional review boards. Investigators must be able to demonstrate a potential for recruiting the required number of suitable volunteers within the agreed recruitment period using the approved study design. Having skilled staff is essential when recruiting and retaining participants and as per the Department of Health (DoH) regulation; this will also ensure that participants are protected. Funders are influenced by ethical safe recruitment and are always looking for skilfully applied strategies to control the bleeding of funds with regard to effective recruitment and retention.

Karen E Wood and John C. Schneider[10] dedicated a chapter in their book to recruitment, retention and compliance, which they consider to be three of the most difficult aspects of conducting clinical trials. They assert that pharmaceutical companies involved in research spend

an average of $1,24 billion in new drug development and therefore the timely enrolment of the appropriate subjects into clinical trials is critical. They highlight challenges around recruitment strategies that could be used to improve recruitment; like advertising, internet search engines like Google and social networks. Other methods discussed include access to medical records, contact with advocacy groups and other health care professionals. In drug development, it is recommended that payment of participants and issues around incentives to retain participants and health benefit to the participant be minimal. When health care professionals, are used for recruitment, they are paid a finders fee. There are two types of incentive fees, one where the finders fee is paid by an investigator to the health care professional and two a bonus aid given by the sponsor to investigators and their staff to enhance enrolment. According to authors payments could compromise the integrity of the trial and be in violation of the institutional policies. They suggest, that for ethical reasons that sponsors cover additional costs of employing additional staff to screen and advertise to boost recruitment in the short term which will impact retention. Personal contact with the same staff member far outweighs the contact of a “finder”.

Retention of study subjects is vital and staff should be aware of the reasons for subjects dropping out and plan for these circumstances. Participants could drop out for medical reasons as defined in the protocol, for reasons such as inability to comply with the protocol, trial related reasons, i.e. the trial is stopped for business, medical or ethical reasons. With these reasons in mind there should be a plan to maximize retention. Participant experience at the clinical site needs to be the best as participants name this as the number one reason for not remaining in the study. Issues like pleasant staff, short waiting times, being treated with respect, investigators taking the time to see them, add value to the study. While being seen by a new doctor or nurse at each visit, being rushed through appointment, not being allowed to ask questions about general health or study related questions and being berated for doing something wrong impacts the study negatively. Some participants leave studies and refuse to give any reason. Karen E wood & John C.

Schneider[10] suggest incentivizing participants by giving ethically approved milestone gifts, mugs, tee shirts, etc. This needs to be budgeted for, giving participants a cup of tea and a newspaper to read may even be enough. Other ideas like reminder calls the day before the visit, thank you notes after a few visits and a birthday card while they are on the study all help to create a supportive relationship. Communication between the participants and the staff is vital; staff should help and affirm participants understanding of how vital they are to the success of study.

When doing intervention studies, retention is nothing without compliance, there is no point in attending each follow-up visit but not “taking the medication” efficacy and safety of the medication will not be measured effectively. It may cause effective medication to appear to be ineffective or visa versa, there will be failure to detect adverse events, safe dosages will be difficult to determine. Reasons for non-compliance must be investigated. Many of the reasons given by participants are; which include that they consumed alcohol over the weekend or that they were taking other medication not on the study protocol and did not want to take both reflecting poor understanding, which could be related to informed consent. Compliance must be managed effectively, having an excellent rapport with the participant is vital, creating a space where they are able to speak to staff without fear judgment. Informed consent should be revisited to ensure that they understand. It was also noted that when staff do not fully understand complex protocols they have participants who are not retained in the study and do not comply. On-going re-training is important staff need to be aware of protocol changes; new staff must be trained before joining the group.

Lessons learnt from literature, reviewed above, highlight that a retrospective analysis of various clinical research studies is imperative to identify ways to improve on recruitment strategies and subsequently impact budget predictions for future studies.

The four studies being reviewed here will include the insights of the issues discussed by these authors and will reflect the actual activity in each study and show how the various study designs, protocol changes, staff allocation and diseases being research impact the ability to recruit and retain participants in research in a specific community. The studies being reviewed here were all based in the township of Khayelitsha.

The Khayelitsha township has a population of 391 748 according to the 2011 Cape Town health district census[11] and was then and still is considered the largest urban settlement in Cape Town. The research site for all studies, in this review, is in an area known as Site B about 22km from the University of Cape Town medical school where the Clinical Infectious Diseases Research Group [CIDRI] is based. This group has actively been conducting observational and clinical research since 2005 within the Khayelitsha Site B healthcare facility. All four studies being reviewed were conducted at this site or at clinics involved in the outreach programme of the healthcare facility and limited numbers at a secondary level and tertiary level hospital who fall within the drainage area of the Khayelitsha township. Over the last eight years' residents of Khayelitsha especially those of site B have come to understand the concept of medical research and appear to be well informed about research processes, their positive response to on-going and new studies give researchers this impression. The area is also closely associated with non-governmental organizations like Doctors Without Borders (MSF) and activist groups like Treatment Action Campaign (TAC) who are also very active in the community and who have been our partners in research projects.

The CIDRI group has supported the healthcare system not only with extra nursing and medical skills, but with foreign funding that has supported and added to infrastructure development. With all these stakeholders in place which include national, provincial and local government, non-governmental organizations, activist groups and academia like the University of Cape Town;

research has been on-going but would not be possible without the volunteers from the Khayelitsha community. The area has health committees who operate on an informal basis in the community. They are the elders in the community, interlaced with a few community activists and local councillors. Prior to every research project they are invited to the clinic to be informed about the new projects, they ask questions and are invited to the annual open research day at the clinic facility. All studies' results and progress are presented at these forums, so as to keep all volunteers and the community informed.

The process of participant recruitment is ongoing and vital; the ability for staff to motivate the community members to voluntarily sign an informed consent and complete the study protocol requires individuals who understand both the study and the community. Recruitment also needs to be well planned, culturally sensitive and respectful of the healthcare programmes which are being implemented and managed by the healthcare service. Staff recruiting, retaining and doing any kind of research activity, were all GCP trained. Additional training was also facilitated to ensure all members of the team fully understood the specific protocol.

Many authors have prescribed a particular format of recruitment; others realize that this process of recruitmentology as coined by Epstein [2] differs constantly depending on the project complexity, community, disease being studied, community exposure and understanding of research, as well as staff member's ability to act on the protocol and identify shortcomings in the prescribed recruitment processes and therefore being able to adapt the prescribed approach.

In this review, each of the CIDRI studies required different strategies due to the different study designs and inclusion and exclusion criteria. By evaluating each study, this review hopes to provide lessons learnt that could be carried from one study to the next as research recruitment memory. This review aims to recommend guidelines for any future studies in the township of

Khayelitsha by answering the following objectives, using Tappens'[5] ten steps as a foundation via a Data Abstraction Tool (DAT).

Objective 1

Was the proposed recruitment strategy followed as per study design and approved study protocol?

Objective 2

Was the overall recruitment impacted by staffing structure and allocated recruitment time frames?

Objective 3

How were study outcomes impacted by recruitment and retention?

Objective 4

TB/HIV were the diseases of study in all four studies, do these two diseases have specific challenges which impact recruitment and retention?

2 Methods

2.1 Use of Data Abstraction Tool (DAT)

This single document (Annexure A) will be used throughout the review of these four studies, to formally collect and present the required study outcomes. To establish the need and impact of protocol amendments, with the use of the DAT; dates of changes to the protocol will be collected from the regulatory file and a description of the change will be noted. Protocol changes made that do not influence recruitment and retention will not be noted.

Monthly recruitment totals will be collected and matched to any staffing changes within the department. Special attention will be paid to appointment and or resignations of various categories of staff; e.g. research officers, research nurses and clinical research workers. This will show the staff compliment, which is the most or the least effective around recruitment and retention.

Three of the four studies in this paper were directly linked to a clinician's PhD and the time frames for recruitment were guided by the protocol of the student and the student's financial contract with the university. By abstracting this data, I will attempt to show if study outcomes of the protocol were met within the dedicated time frames and if the protocol study outcome was achieved.

3 Study 1

3.1 Introduction

Isoniazid plus HAART to prevent tuberculosis in HIV – infected persons, NCT00463086[12]

The study was a randomized control trial to be conducted in a pragmatic setting, which was embedded in the activities at the clinic. This study was conducted at the peak of the roll-out of Anti-Retro-Virals ARV's at this clinic which was led by MSF, one of research partners on the trial.

3.2 Results (Application of DAT)

This study utilized several databases to ensure that all research partners had access to the information. The DAT information was therefore not extracted from the database, but from the screening and enrolment logs which documented dates of screening, dates of enrolment and all relevant study activity. Protocol and all study records have been archived in the secured archived facility within the University of Cape Town. Application for access to these documents was made and with the use of the DAT for the extraction of the information. Permission was granted by the custodian of these records, Professor RJ Wilkinson. The outcome of this application is reflected in Table 2. Personal experiences of management of the study were also considered.

Screening for this study commenced in November 2007, which could be a good or bad departure as starting around the 16 December each year Khayelitsha residents leave Cape Town for a prolonged break in the Eastern Cape to attend or participate in many Xhosa cultural events. This trial was started and recruited 68 participants over a period of 6 weeks in November until mid-December, this gave the study team an opportunity to reflect on the recruitment practices and pragmatic logistics of the trial. The recruitment plan was to have the entire clinic staff supported by the research team recruit and follow-up participants as this study design was a pragmatic one. First participant was recruited in November 2007 and the last one twenty-four months later in November 2009, study staff were employed two months prior to starting and these two months

were used to protocol train both study and clinic staff. The recruitment target was achieved but many peaks and dips are noted during the process; the highest number was recruited in the winter months when HIV positive patients tend to present with minor ailments and opportunistic infection. The highest month of recruitment was October 2008 with one hundred and forty-nine and the lowest in December of the same year with only two recruited. The protocol expected eighteen months for recruitment, but working with a disease like HIV when medication is being rolled-out for the first time had its issues which the study had to accommodate. Follow-up continued for fifty-two months, the staff compliment changed often with the highest number if nurses employed exclusively on the study was four and low as two. It appears at a glance that this study was always well staffed and the lead investigator who managed the study was always available. Retention was poor due to the fact that the lost to follow-up being higher than anticipated. All protocol amendments were well timed, the first was done before the study was activated, the second after five months into the study and the recruitment number improved post this amendment, the third was done at the time the clinic usually slows down. The final change was submitted during the retention phase.

3.2.1 Recruitment as per protocol and protocol changes

The recruitment target, as per protocol after sample size calculations was to enrol a minimum of 1204 and a maximum of 1445[12]. Patients already established on ARVs and those about to start ARVs would be enrolled and within these 2 groups of volunteers would be randomized to either 12 months of INH or 12 months of placebo. They would be monitored for study outcome for 12 more months after the last participant had stopped taking the study drug. The recruitment strategy was to be preceded by mass education about IPT (Isoniazid preventative treatment for TB). This was done in all waiting areas at the Site B healthcare facility, patients were then invited for smaller group discussions with study staff if they were interested in joining the study or wanted to have

any more study information. Patients who were in the process of being counselled as per ARV programme were also counselled on IPT during their three prescribed counselling sessions. These sessions were done by routine clinic staff and study counsellors. This was an opportunity for the clinic or study counsellors to refer eligible interested patients to the rest of the study team for formal introduction to the study and possible informed consent. For patients who were already well established on ARVs and were attending the clinic for their routine follow-ups, they would also receive the mass waiting room TB/HIV education including information about IPT. When seen by the clinic nurse or doctor they were given the opportunity if they were interested in speaking to a study staff member about the study. They would then be given more information about the study and an informed consent document to review at home or in the waiting room. It is important to note that some of these patients were well established on ARVs and had already returned to the workforce.

Some of the recruitment strategies used was the local area radio station, Radio Zibonele 98.2 FM. Radio Zibonele was established in 1993 in Khayelitsha Cape Town as a home-made radio station. The lead investigator offered to be interviewed about general health issues on the radio station every Tuesday in the regular health slot, so that listeners could phone in and ask for advice. Once the trial was about to start an excellent relationship had been built with the listeners and the counsellors who were the recruiters then continued to use this platform to offer advice and explained to the listeners about the trial being conducted at the Site B clinic in KY. No study information flyers were produced or circulated in the community as our partners on this study; who had been working on the de-stigmatisation of HIV in the community prior to the study starting felt that access to the group of patients attending the clinic was sufficient. This was important information for the study team, as working together with our partners was critical in conducting the trial.

Initially everybody was consented and then screened for TB, which was an exclusion criteria. After ICF, the study protocol required a very intense TB screening process to ensure the participant was eligible for enrolment, which included folder review for blood results, (last CD4 and viral load) symptoms of TB, history of TB and current TB treatment. All participants who were still eligible after this process would be fully screened for TB as per protocol case definitions; inclusive of the collection of sputa for TB culture. The initial step of this phase resulted in many patients being consented for the study only to discover that they were either not eligible because they were active TB cases on TB treatment or were not truly interested in the study. In this initial phase, the study team accessed patient records with the consent of the patient; accessing records ahead of study procedures helped to eliminate a group of participants who recently completed TB treatment or had other chronic conditions which excluded them as per study protocol. The clinical research workers noted that many of the volunteers who were being consented were later found not to be eligible, they brought this to a study meeting and after the lead investigator reviewed the screening log it was confirmed. It was then decided that the study team's time would be more efficiently used by first eliminating these candidates before formally approaching them to join the study. A protocol amendment was requested from ethics specifically for this activity, and their folders were reviewed and marked "not for ART_IPT study."[12] The amendment was submitted as a letter to the ethics committee chairman and expedited, no recruitment time was lost waiting for response from a full ethics committee.

The participant recruitment and assessment of eligibility as per protocol and the responsibility of recruitment was allocated to the study counsellors, research nurse and research clinicians. To recruit the required numbers effectively, the lead investigator planned to mirror the clinic activities as closely as possible. The participants were randomized either to the INH or placebo arm of the study then the process of retention began. Once enrolled the participants had to attend the clinic every 28 days for 12 months as part of the study protocol (as illustrated in Table 1) those newly started on ARVs also had to routinely attend the clinic every 28 days as part of the ARV

programme which suited the study protocol. The trial matched their study visits with the routine clinic visits, which assisted with the retention to the study. However, those already established on ARVs were attending 2 monthly and the trial protocol required them to attend more often, which presented a problem for some participants. It is important to note the recruitment plan already included a retention plan.

Table 1: Illustrating differences in routine ARV clinic and Isoniazid plus HAART study visits.

Newly started ARVs clinic regime	14 days of starting ARVs	28 days after starting ARVs	Every 28 days for first 12 months of treatment →	Routine clinic →	
Newly started ARVs trial regime	14 Days after starting Study drug	28 Days after starting Study drug	Every 28 days for 12 months while on study drug and 12 months after study drug had been stopped	ALT done on day 28 and every 3 months →	Study bloods →
Established on ARVs clinic regime	2 monthly visits	Extra visits if patient had issues with adherence, side effects, or when routine CD4 and viral loads needed to be done		Routine clinic →	
Established on ARVs clinic regime	14 days after starting study regime	28 Days after starting Study drug	Every 28 days for 12 months while on study drug and 12 months after study drug had been stopped	ALT done on day 28 and every 3 months →	Study bloods and extra visits →

This system continued throughout the study as clinic staff were very focused in achieving the set target to start as many people on ARVs as required it. The clinic numbers rapidly increased therefore, anybody who was stable on their ARVs for more than 6 months with good adherence, a responsive increase in CD4 count and matching viral load suppression, was transferred to the "club" system. They could then attend 3 monthly sessions at a local community hall closer to their homes and collect medication. They then only attended the clinic when they required their 6 monthly CD4 count and viral load bloods to be done. This did not have as strong an effect on

follow-up visits as initially thought, as many of the participants with whom the study team had developed an excellent rapport were happy to attend a study visit every 28 days, which took about 30 minutes. Another challenge the trial faced was that the participant was not always seen by research staff and as part of the pragmatic system they would be seen by the clinic staff and would on occasion miss protocol-required activity. This resulted in study staff, who could have been recruiting new enrolments, spending lots of time recalling participants to come back for study specific activities and adding extra clinic visits for these participants.

3.2.2 Staff Allocation and changes

This pragmatic trial required teamwork from the entire clinic workforce, not only the study staff. A memorandum of understanding stipulated how study team and their partners would work as a team, and who would be the co-investigators. Partners included nurses and doctors employed by provincial health, as well as MSF doctors, nurses, and counsellors.

The staff complement on this trial included: the lead investigator, one research officer, one study coordinator (nurse), one senior research nurse, one research nurse, one clinical research worker/ recruiter and one office administrator employed by the University of Cape Town. The MSF team at the start of the trial consisted of two counsellors /recruiters and one nurse, they would be supported by the clinic staff as part of a pragmatic design. Early in the study a consultant quality assurance person visited the clinic one week per month to institute quality assurance plan with a quick corrective action process on source documents to prevent errors going unresolved early in the recruitment process. This proved very helpful and was done pro bono. Clinic staff did not always appreciate the corrective action process, but soon saw the value of it and slowly embraced the process this resulted in a decline in documentation errors. This improved documentation during the study both general clinic staff and the research team appreciated that the quality

assurance staff highlighted research activity to be done at each visit. Thus, making the pragmatic study design more effective, staff did however require training on an ongoing basis.

The protocol related training caused some anxiety among non-study staff because the staff felt it had increased their workload, which it did as it was now a requirement for intensive TB symptom screening as per protocol amendment with clear documentation in the hospital folder and referral to research staff. After many joint training and information sessions, general clinic staff accepted that the amendment was to the benefit of all patients and embraced the process. During the on-going Radio Zibonele sessions the value of being asked to be tested for TB was emphasized and encouraged. This was also highlighted in the mass education session in the waiting rooms, which resulted in many people asking for a “TB test.” While this was an important benefit for the patients, it also impacted the expected pace recruitment and resulted in all the extra training decreasing the amount of time staff could spent on recruitment. Nurse contact time also increased and clinical research workers who were involved in consenting now performed sputum inductions to collect sputum on all those being worked up for TB.

Another factor which affected the study was that participants who were recruited into the “not yet on ARVs group” could have started ARVs by the time the TB culture results were available, thus decreasing the numbers in this group. As previously mentioned this trial was being done at a clinic where ARV rollout was being vigorously done and the study activity did not want to be the reason for delaying this process. Therefore with the earlier protocol [12] amendment defining the length of time on ARVs was more clearly defined; from newly started on ARVs to newly started on ARVs but not on ARVs for more than three months, if more than three months the participant would be reclassified as established on ARVs. Testing all patients for TB was now no longer only a study required but mandatory throughout the clinic. All staff had to be trained to ensure that they understood the TB work-up and the study inclusion criteria.

Retaining staff in the local healthcare environment is always a challenge, as nurses have many opportunities both nationally and internationally and salaries in the different sectors become more competitive. The original group was one study co-ordinator (nurse), one research nurse from the University of Cape Town and two research nurses from MSF. The study co-ordinator left the study, another senior research nurse was employed by UCT, the two MSF nurses left at different times and the vacant post was filled by one enrolled nurse who required closer supervision and training in phlebotomy. During the life cycle of this trial, a medical research officer was employed for one year, but also left for better opportunities and after a short time without this position being filled, it was clear that staff required more support and another medical officer was employed later. This activity in the staff turnover is illustrated in Table 2, although it appears not to have affected recruitment, as there was always sufficient staff even if they were sometimes at different levels of protocol awareness. The lead investigator became fully responsible for the clinical activity and the part time Project co-ordinator was soon employed full time.

3.2.3 The impact of study outcomes linked to recruitment

Objective 3 was achieved in this study as the recruitment plan included a retention plan even though it had some challenges. Many HIV positive patients had no obvious signs of active TB infection or disease due to being immuno-compromised they were at risk of being enrolled in the study and violating inclusion criteria. Intensive symptom screening was done on all volunteers who gave consent for the trial, and spontaneous or induced sputum samples were also collected, with microbiological sputum results returned in 45 days before TB could be confirmed or rules out. This slowed down recruitment as the intensive symptom screening was rolled out through the entire clinic in keeping with the pragmatic study design; however, this was a huge benefit to the trial as this process reduced the risk of enrolling participants onto the study who had TB. The risk of therefore starting TB patients on INH (mono therapy) or placebo was greatly reduced. The

protocol change was made in September and training activity was implemented over the “slower” months of late October and November. As reflected in Table 2, recruitment gained momentum as soon as the clinic re-opened in the new year

Discussions to implement this amendment effectively were held with all stakeholders, and this resulted in temporary pause over the slower December period in recruitment to train staff and re-evaluate the processes. Clinic nurses considered this as extra work, which should only be done by research nurses. More training proved to be effective, as all medical staff and counsellors understood that this new system would benefit all patients attending the clinic and those being started on ARVs. The more vigorous TB screening assessment prevented patients being started on ARVs if they had active undiagnosed TB. Together with all the stakeholders involved at the clinic this process was successfully implemented. A more intensive TB screening process became mandatory for the entire clinic, and new clinic screening documents were designed by the group and paid for by the study group (an unplanned but necessary expense). Training staff in the correct use of this tool was vital. The lead investigator allocated a large chunk of her time ensuring all the training was done and everyone completed the document in the same way. The major change to the TB screening approach was the way the questions were asked. It changed from, “Have you had any of these symptoms for more than two weeks?” to, “Have you had any of these symptoms in the last 10 days?” It was known as the “any cough” question, this increased the workload at the clinic but screened out all TB patients before they were even approached for consent to the trial; prevalent TB was identified and treated. Though the intensive screening did slow down recruitment, the benefit to both the study and patient population outweighed the negatives. Our staff and the clinic staff were also trained in a new skill of sputum induction, as not all patients who reported a cough were able to produce sputum on the day of the clinic visit. Participants, who were recruited and consented, were sometimes enrolled before sputum results were available. If results came back positive their study drug was stopped and they were referred

to the TB clinic. This was done in agreement with all the stakeholders. The bigger impact on this was that patients who were eager to start ARVs were more forthcoming with TB symptom information and those already established on ARVs wanted the assurance that they did not have TB. Though the screening was implemented to ensure adherence to the study protocol, the real beneficiaries were the patients themselves.

3.2.4 Retention

To retain participants' in the study, especially those who were considered stable on ARVs and who had returned to the workforce was the most challenging group. Research staff started to work much earlier in the mornings than the clinic staff, so that participants could be seen before they went to work. The modification to the timetables again impacted the team numbers as staff who started earlier had to leave earlier, and our workforce became smaller in the afternoon on specific days when staff were given back their time. This was the challenge of recruiting and retaining simultaneously. MSF employed a medical officer to support the team, the medical officer would review participants when staff had to leave early in lieu of the mornings when they came to work early to attend to participants before the participants went to work.

Managing follow-ups with adverse events proved challenging and took lots of discussion, education and cajoling of study staff to ensure that none were missed. Adverse events, even though they were not always study drug related, as they were "common" ARV side effects, which as per protocol, had to be documented and acted upon. A grade1-2 rash noted at 2 weeks on ARV therapy would only be monitored in the ARV service and not treated as an adverse event. The clinic staff especially felt constantly challenged by the research team when they were reminded not to miss adverse events, as they on occasion felt their ability to manage patients on

ARVs was being undermined. For this reason, study participants were sent to the study team even if they did not have an adverse event. This overburdened the study team who spent the full day reviewing participants who could have been seen as part of the pragmatic system. Study participants ended having to wait long periods; due to the increasing numbers and ineffective bookings of follow-up appointments. This caused some unhappiness and increased the potential of participants missing their next appointment. It also resulted in study nurses being taken away from on-going recruitment process. The employment of the full time medical officer six months into the trial; from MSF was very useful in managing this situation in a more productive way. Her joining the team had a positive impact on the dynamics between clinic and research staff. She reviewed all possible adverse events and feedback to the clinic staff always complimenting them on those they had identified.

Balancing on-going recruitment with retention and study drug compliance was not easy. It took many hours of input from the medical team to keep the study team motivated. The resetting of monthly recruitment targets, follow-up plans and compliance management strategies, as illustrated in Table 2, also required attention. It is important to note, that the study staff preferred to be led by the medical officer or the lead investigator. After eighteen months, the study coordinator required surgery and chose not to return to the post, which created another disruption to trial processes. These disruptions required staff to push harder once they had settled to continue achieving targets, which is evident as the numbers dipped the two months after the departure of the co-coordinator month eleven and twelve and then increased in month thirteen.

3.2.5 Descriptive summary of recruitment and retention trends (Table 2)

There were twenty-six months of actual recruitment that peaked in 2007 to above one hundred per month, over the months of June to October and in 2008 the peak of over hundred per month occurred from June to February. The overlapping months in both years are the two wet months in Cape Town, June and July. These are the two months where the clinic traditionally sees higher numbers as patients present at the clinic with chest infections, coughs, colds and flu symptoms. This increase in numbers of people seeking health care, gave the study staff a large captive audience where they informed the waiting room about the study and where mass TB education was presented did every morning.

Months with lower recruitment numbers were immediately noticeable after the protocol training and could be attributed to a settling in period. During this time; new trained staff found their confidence and developed the skills of recruitment and became familiar with the detail of the study protocol. November 2007 showed a 50% drop in recruitment numbers, traditionally the time, when the community goes to the Eastern Cape During the month of November patients are given a two-three months' supply of ARVs with an appointment to return the following year. These patients are often very intent on receiving the increased supply of chronic medication and not in necessarily joining research projects. January is also expected to be a slow month and during this month staff also take their annual leave and only return to work in the 2nd week of January. November 2008 was also a very slow month for recruitment, but fortunately the study had reached their target sample size and more participants were not required.

From a staffing perspective, it appears that the employment of the projects' co-ordinator and study clinicians impacted recruitment positively as they did the general study administration and all the study related quality assurance. This allowed the rest of the study team to continue recruitment.

The study co-ordinator was not replaced as the team found the clinicians who were on site everyday could manage the study.

While working on the study we, the study team felt and discussed that the protocol amendments and re-training slowed down recruitment, but on reflection it appears it did not impact the study negatively as post re-training and protocol amendments the recruitment numbers increased. Noted also that amendments were done at the traditionally slower months in November, December and January.

Retention also impacts recruitment as both these activities both require appropriate division of labour to maximise both activities. This study had to contend with high numbers of deaths as many of those seeking health at this clinic were usually in advanced stages of AIDS, these participants who had enrolled in the study did not complete the follow-up as per protocol. Many people come from other provinces in South African to seek access to ARVs, and when their own provinces acquired access to ARVs many patients requested transfer back to their local provincial clinic, which also resulted in higher than expected lost follow-up. In these early days on the ARV role out programme many people had side-effects, this study documented all adverse events from ARVs as related to the study drug. The study drug was usually stopped in these cases and the participants were also lost to the study. It should also be noted that reporting of these adverse events did not impact recruitment adversely.

Table 2. Recruitment and retention throughout the study 1

3.3 Discussion

As a pragmatic study conducted in a clinic, which at the time was focused on the roll-out of ARVs, this study could recruit in excess of one thousand two hundred participants in twenty-six months and follow them up in for a further twenty-four months. Two protocol changes were made to ensure targets were reached., these changes implemented effectively by the lead investigator and did not negatively impact the recruitment of retention. One focused on the improvement of retention, by synchronising the follow-up visits with that of routine clinical care. The second of intensive case finding TB, but this was implemented over the quieter months of November and December. Many recruitment strategies were implemented, recruitmentology as a new discipline was developed as described by Epstein [2]. A challenge of this pragmatic study was the use of shared space, which is common practice at the clinic. The research arm of this system required sufficient space to conduct informed consent and maintain confidentiality. The recruiters developed skills to and “created” spaces to complete confidential research documents with the participants to ensure the recruitment process continued. The recruiters or CRWs functioned well and put the interest and health of the participants first as they developed a relationship with them. Which was beneficial for the twelve month study drug period plus the long twenty four month follow-up period.[4] Staff at times displayed low morale due to fatigue and the long follow-up period. During this study, and it was especially evident when participants did not arrive for appointments due to relocation and death. Staff were concerned by the inability to maintain the sample size as discussed by Shapiro[6]. The challenges experienced by the staff because of the pragmatic study design at the time appeared to negatively impact recruitment, but on assessing the monthly recruitment totals this is not reflect.

The question therefore remains:” Could they have achieved the study target sooner if it were not for the study design?” Although the pragmatic study design had its challenges the target were not

adversely impacted, this project changed the clinic patient management for the better. Although the retention process was affected by factors such as geographic relocation of participants, death and adverse events, it did not negatively impact the study outcomes as the study showed 37% benefit to patients using INH in both arms of the study, which was adequately powered. TB/HIV research is challenged by many factors but community organizations worked hard to encourage patients to be tested for HIV and to present to health care facilities if patients suspect TB. At the time this study was conducted there was a great deal of community activism with regards to these two diseases and recruitment was positively affected as noted by the consistent recruitment targets achieved. The presence of research medical officers supporting clinical care and research administration ensured minimal disruption in recruitment and retention.

A review of this study reflects that the proposed recruitment strategy and study design although challenging achieved the set targets. Also, that staff changes caused discontent in the team, but current team members always remained focus and achieved the goals. Even though this study was marred by deaths, adverse events and re-loactions, it was sufficiently powered to achieve the study outcomes as the team as able to keep the rest of the participants motivated enough to complete the study visits. As the study required HIV positive participants the recruitment was enhanced by the ability to access this group and work within the clinic structure.

4 Study 2

Increasing prevention and treatment of TB through development of a rapid, sensitive and affordable biological marker (genomic or proteomic) for diagnosis of TB and HIV positive and negative populations. (HREC 012/2007)[1]

4.1 Introduction

The main focus of the study was to identify latent TB biomarkers plus the dissemination and reporting of knowledge and recruitment to industry partners for the future development of affordable diagnostics based on the programme of biomarker discovery (Protocol HREC 012/2007)[1]

The approved protocol had a sample size of 300 with 6 groups to be recruited, 50 participants per group. All groups were TB/HIV related.

1. *TB^{+}/ HIV^{-}*
2. *TB^{-}/ HIV^{+}*
3. *$LTBI^{+}$/ HIV^{+}*
4. *$LTBI^{+}$/ HIV^{-}*
5. *HIV^{+} with an opportunistic infection other than TB*
6. *HIV^{+} with an acute and chronic infection other than TB*

Protocol proposed recruitment schedule offered no time lines, but would be guided by the related PhD and Masters projects affiliated to the protocol. The protocol clearly states that the target population would be 21 years and older and be recruited from specific health care facilities, viz. Khayelitsha TB clinic, MSF HIV clinic and GF Jooste hospital in Mannenberg, Western Cape. These sites have drainage areas; which overlap and GF Jooste serves as a referral centre for clinics in the Khayelitsha area. Permissions were requested and granted by the lead investigators on behalf of the PI from the provincial health authority who manages the HIV programme and the

local city health authority who manages the TB programme. The provincial authority also manages the services of the secondary level hospital GF Jooste; therefore, the permission would allow the protocol activity to include GFJooste as well.

4.2 Application of DAT

All data related to this study was captured on Filemaker 9.0 and stored on the UCT network and was password protected. Access to this database can only be gained via the data manger, who was given delegated authority by Professor Wilkinson. All requested data is sent in an excel format with only the variables requested. Application of the DAT facilitated the population of Table 3. Personal experiences of management of the study were also considered. Recruitment plan and changes were not evident as no time lines for recruitment were indicated in the protocol. Recruitment and follow-up, were completed in thirty-six months' monthly peaks and dips showing no pattern. Amendments that's affected recruitment were moving to an additional site and in the specific increase of samples site had little impact as timelines were not an issue. The staff compliment increased during this study, this was led by the study need and therefore did not negatively impact recruitment or retention. Study contact was a maximum of three months with telephonic contact later. Main challenge was staff management as lack of targets sometimes resulted in decreased enthusiasm.

Community recruitment went above forty in a random four months and below ten in another unrelated six months, this could not be linked to the usual Cape Town holidays and on reflection can only be linked the work ethic of the recruiters and lack of adequate supervision. The hospital 1 recruitment peaked at month 25 and here again it can only be linked to recruiter skills and work ethic. Recruitment in the hospital is very different and staff need to be confident to approach an ill patient. Amendments were well timed and show an increased in recruitment as was the purpose of the amendment, one to add an extra site and two to increase the sample size.

4.2.1 Recruitment as per protocol and protocol changes

The first participant was recruited in 05 November 2007 and the last 18 August 2009, followed by a second phase started on 03 January 2010 and consented the last participant on 15 July 2010. Reasons for participants refusing to participate were not recorded. This process yielded 452 (n) in phase 1 and 190 (n) in phase 2, a total of 1194 participants were consented and an application was made to ethics to increase the sample size.

Recruitment so late in the year was not very effective as clinic activity slows down dramatically due to the mobile KY community, but recruitment at GF Jooste hospital continued, as these were in-patients, who presented for care because they were ill. The few participants who were recruited from the community helped the study team to sort out some teething problems and to work on strategies to approach recruitment. All staff working on this project had not worked in research before, as a new study the research group employed 2 qualified general nurses and did in-house training with them on an ad hoc basis while the protocol was implemented. It should be noted that the medical research officer who led this study had not led a clinical research project before, so the entire team was on a very steep learning curve. As the study recruited and followed–up, more participants, a clinical research worker and an enrolled nurse were added to the group. All staff learnt about research while on this project. Although important for capacity building it came with challenges one of them being a slowdown in recruitment as new staff had to be trained and retrained and allowed to become more confident.

Groups 5 and 6 were recruited from GF Jooste Hospital, as per protocol. GF Jooste is a secondary level hospital based in the Cape Flats (Athlone Health District) in the greater Cape Town area. The recruitment started 03 January 2010 and completed 15 July 2010. In this area, the study had 1 research nurse and many hospital doctors, who were aware of this project as well as other

projects being done at the hospital. The relationship with the staff and their awareness of the research is of vital importance. On daily basis, the research nurse reviewed all the admissions from the out patients department, the accident emergency unit and the ARV unit matching potential admissions with the inclusion criteria and per the approved protocol. This nurse had to review and interpret all laboratory tests done at admission and those done after admission with special emphasis on the microbiological results to ascertain that they did not have TB or that TB diagnosis was confirmed. Most patients at GF Jooste hospital are investigated for TB and the samples are sent to a central laboratory. For this reason, the nurse has to be familiar with the computerized National Health Laboratory System, to access these results. This system required regularly checking to ensure that patients with TB were included in the correct arm of the study. If any volunteers were consented and found not to be eligible, they would then have to be excluded and replaced with eligible participants.

Results would take up to 45 days to have TB diagnosis confirmed and therefore lengthened the period of recruitment. This period was standard for all studies being done which required a clinical work-up to exclude pulmonary tuberculosis. A total of 100 participants were required for groups 5 and 6. This required a research nurse who was an independent worker who could work well within a group of non-research nurses. This incumbent was well suited for this type of solitary work and managed to achieve set targets. Non-TB patients became more difficult to find and permission was sort from another provincial hospital to access non-TB patients. Ethics had to be informed, but it did not require a protocol amendment. Although this was not an amendment, a slowdown of recruitment was noted at hospital 1 as the research nurse worked hard at the forging of new relationships and understanding the new systems and personalities at the new facility. This is reflected in Table 3 during the months June to September in year one of recruitment. The new facility Groote Schuur Hospital, (GSH) was a hospital the CIDRI group had worked with before while the transition was slightly bumpy, it was uneventful.

Recruitment started at the GSH oncology unit six months into the study. This was one of the units where GF Jooste referred their Kaposi Sarcoma patients for further treatment. This required follow up from the research nurse if the patient had been consented for the study at the referring hospital. Patients were familiar with the research nurse and soon it was the participants who were recruiting by word of mouth and sharing information about the study with other patients in the ward. Potential participants asking about the study approached the research nurse. While working in this department it was noted that the ward patients could potentially be a source for HIV negative and positive patients who were being routinely screened for TB and HIV prior to the commencement of chemo-therapy, but these patients were because of their condition more medically compromised and not always eager to participate in the research.

4.2.2 Staff Allocation and changes

A process of staff awareness at all health centres had to be carried out by the lead investigator. Clinical staff had to understand the role of the research staff and the purpose of the research, the impact it will have on their day to day work as well as the impact on the patient/participant. As this study had 6 groups and was done in 3 facilities with 2 research nurses (later 3) and 1 Clinical research worker (CRW) the strategies were slightly different for each group.

For groups 1,2,3 and 4, the strategy started with the staff awareness at the clinic level, building a relationship with staff is vital, offering and giving clinical support and having staff understand the roles and workloads of the research nurses and other research staff is important. Research staff worked closely with, ART readiness counsellors, ART adherence counsellors, TB counsellors and TB care workers. The focus of research staff was to inform the general population sitting in the waiting area about the study and this was accomplished by constantly giving talks in the waiting area so that potential participants would be aware of the study and the inclusion and exclusion criteria. Nurses and doctors working in the clinics would also inform patients about the study and

refer them to research staff for further information. Once contact was made with the participant the informed consent process would be initiated with the patient on a one-to-one basis allowing the patient to volunteer to be part of the study. In the TB confirmed groups research staff worked closely with the existing TB facilities and constantly reminded staff of the presence of the study, building relations with this group was vital to the success of this study. These relationships were not always easy as the presence of research staff can be viewed as disruptive; it required skilled research workers to ensure that this relationship was cultivated and maintained over time this helped with the access to documents like the TB register and patient details which were important for the research staff. In this study, the research team had no resignations, the addition of a research nurse was well planned and added value to the recruitment process.

4.2.3 The impact of study outcomes linked to recruitment

Noted challenges were extra study activities; which included CXR if not yet done, 2 sputum samples, sent for AFB smears and MTB culture, some would require a sputum induction process not routinely done and beyond normal care; 40mls of blood would be drawn for only study purposes. This again had minimal negative impact as participants were referred for CXR, the CRW did induced sputum collection and nurses supported each other doing the blood draws. The fact that the recruitment timeline for this study was more fluid; staff merely recruited as participants became available and responded to their strategies.

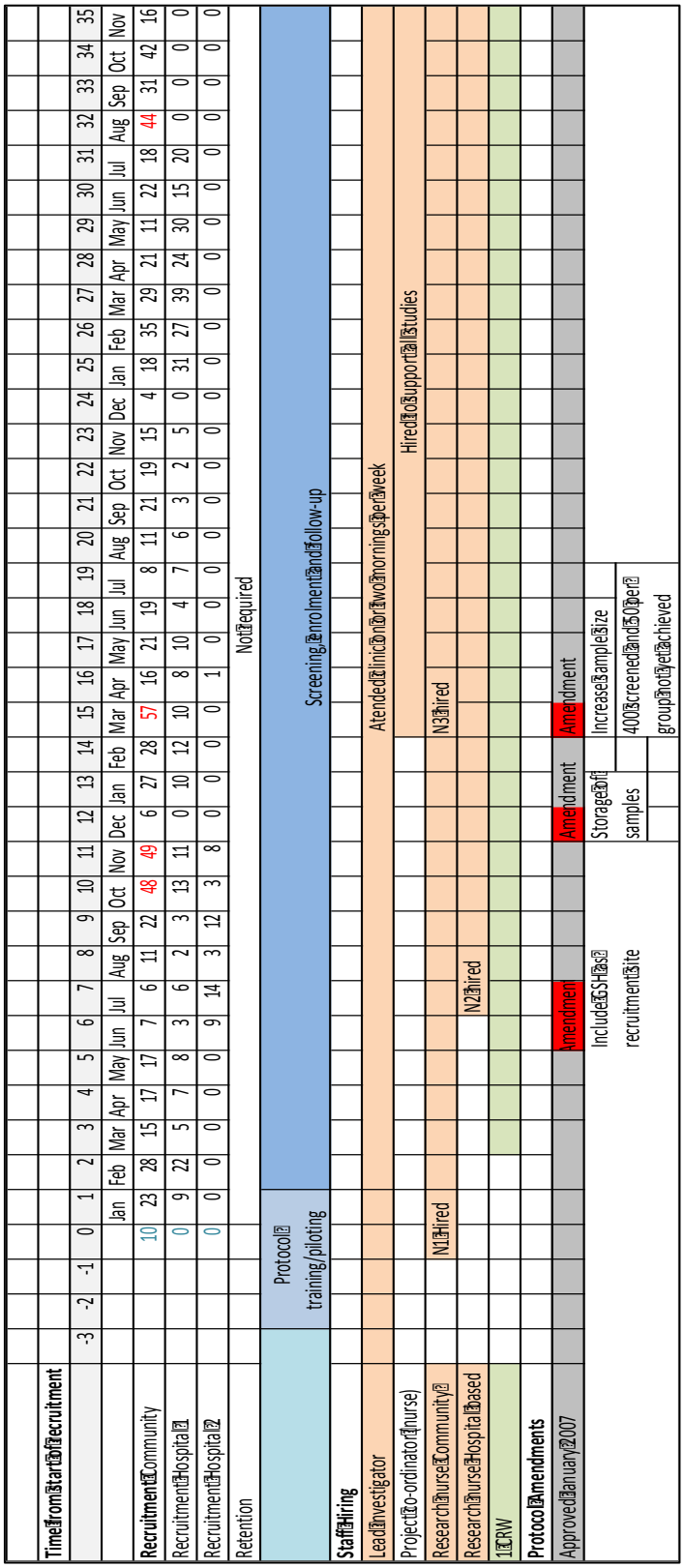
4.2.4 Retention

The only follow-up required was the reading of the skin tests and the second visit for TB workup results. A CRW was assigned to contact participants telephonically to remind them to attend of

their skin test reading with an excellent response. Those who did not return for their TB work were approached when they come back to the clinic for routine care.

4.2.5 Descriptive summary of recruitment and retention trends (Table 3)

Table 3: Recruitment and retention throughout study 2



Total recruitment and follow-up took 35 months, no visible trends noted with recruitment, it appears that no attempt was made to exceed targets if any target were set at all. The months of October and November in year one, March of year two and August of year three recruitment of over forty participants was achieved, but this was not consistent. Setting targets could have shortened the recruitment phase. Although these research nurses worked under supervision, the lead investigator only visited the clinic or hospital one or two mornings per week and recruitment was static. In the month, an amendment was made to increase the sample size due to slow recruitment there was a slight peak in recruitment to above fifty for a single month. The addition of the third site yielded only fifty participants who were the much-needed HIV^+ group with an opportunistic infection other than TB and the HIV^+ group with acute or chronic infection other than TB. Although this was a small group it augmented the existing participant numbers bringing the total close to four hundred recruited as inpatients. Staff complement remained constant, but closer supervision may have decreased the recruitment period, from personal involvement in this study it was noted when the PhD student leading this project focused on academic obligations. After recruiting and consented one thousand one hundred and ninety-four participants, only six hundred and forty-two were found eligible for the six designated groups. This questions the effectiveness of the recruitment strategies and the need for closer monitoring of recruiters. No protocol amendments were noted to have disrupted the recruitment process, although an amendment to increase the sample size was required. The employment of extra staff was done as the workload increased and was therefore a benefit to the recruitment process. Finance and financial implications are not being discussed in this paper, but any extension in recruitment always negatively impacts original research budgets, as staff, for example; research nurses have to be paid during this extended time.

4.3 Discussion

While working at a community clinic, a secondary level and tertiary level hospital was challenging it, however, proved to be effective. It allowed the study to fulfil all the required categories as required in the protocol, as noted before this protocol had no stipulated recruitment timelines. Recruitment into all the groups proved to be overwhelming for staff as each group had different inclusion and exclusion criteria, “new” participants had to be recruited if TB results required the participant to be moved to another study group. This required staff to pay attention to detail and ensure volunteers were allocated to the correct group. In some cases, it could not be done immediately as results confirming diagnosis where not immediately available. Research nurses had to later confer with the research medical officer and allocate the participant to the appropriate group. They then needed to assess their new targets and recruit accordingly. This “moving” target was on occasion challenging for some staff members.

This study protocol had not paid too much attention to recruitmentolgy as a science, but focus more on the science of finding the biomarkers. The CIDRI research team learnt lots about the need for including recruitment plans in the protocol, setting targets once recruitment has started and ensuring better staff supervision. This study therefore laid the foundation in the group to writing less fluid protocols, focus on supervising staff and setting of targets. Although the study outcomes were met they it could have been completed in a much shorter time. Due to the study having 6 groups covering all presentations of TB/HIV inclusive of other infections as well, we considered that the net was thrown to wide for the recruiters.

5 Study 3

5.1 Introduction

The Impact of Seasonal Vitamin D Deficiency and Vitamin D Supplementation on the HIV-1 Immune Response[1]

Due to the highly seasonal pattern of UVB exposure and the summer peak, Cape Town, South Africa, is an ideal place to evaluate the seasonal response to Vitamin D. Inhabitants are at risk of vitamin D deficiency in winter months. This risk is enhanced in individuals with dark skin pigmentation as melanin reflects UV. This study aimed to determine whether seasonal vitamin D deficiency occurs in two healthy young adult populations with moderate-to-dark skin pigmentation in Cape Town, and whether vitamin D supplementation can correct deficiency-associated immune responses. Approved Protocol 003/2013.

5.2 Application of DAT

All data related to this study was captured on Microsoft Access and stored on the UCT network and is password protected. Access to this database can only be gained via the data manger, who was given delegated authority by Professor Wilkinson. All requested data was sent in an excel format with only the variables requested. The database also had data from our Tygerberg collaborators who recruited the moderate skin toned group. These participants will not be included in this analysis. Personal experiences of management of the study were also considered. Recruitment timelines were guided strictly by the season, all participants could only be recruited after the summer and before the Autumn equinox as the days would become shorter resulting in less opportunity for sun exposure. All participants were successfully recruited in the allotted 6 weeks. The follow up could only be done in the month of August after the winter months; further follow-up after 6 weeks of vitamin D which was not part of the initial protocol occurred from September into October. The follow-up and retention had many challenges.

As reflected in Table 4 the first 51 participants were recruited with ease during the month of February and March 2013, both warm summer months with young participants between the ages of 18-25 years. Recruiters used the strategy of “bring a buddy”. Many of the participants were recent school leavers who were currently unemployed so they eagerly brought a buddy along and introduced them to the recruiter. Although staff recalled participants in June to remind them of the study activity, by not being able to consent them for the pending protocol amendment, staff felt negatively impacted the retention in the winter, which was discussed at the post study debriefing. Due to the small sample size and specific period of recruitment, all staff working on this project were also involved in other larger studies being conducted by the CIDRI group. This study had less flexibility for recalling defaulters due to the fixed window period which was strictly guided by the winter season. It was felt that young healthy participants were less interested attending the clinic in the winter. At the countless home visits to participants many were found to have started tertiary education classes in the June (2nd semester) and were therefore unable to return for the follow up.

During the third visit the participants were requested to take Vitamin D for six weeks, some were very apprehensive on their return visit because they had not taken it as prescribed. A few participants had to be postponed, as they had not taken their last tablet yet. Research staff gave them their last tablet and re-booked them for a week later.

5.2.1 Recruitment as per protocol and protocol changes

The team visited the local youth centre, as the target age group was 18-25 years, they made announcements at the local day hospital and to the participants attending the other active research projects being conducted by the CIDRI group. The inclusion criteria were simple: they invited dark-skinned, healthy men and women between the ages of 18-25 years who were willing to be tested for HIV. The response was overwhelming, which allowed the research team to be selective. Mass information sharing about the study was done and was followed by an open question and answer session. This worked well with this younger group who were open to freely discuss

most health issues without much prompting. Only those willing to have an HIV test and whose skin was dark enough were finally consented in a one-on-one session. Once they were consented they were given appointments to attend from 0900 in the morning on the specified study days. They were informed to be punctual as they would have bloods done which would have to be taken from the clinic to the laboratory which was 30 minutes away. All the bloods had to therefore be taken within a 30-minute period and had to be in the laboratory 60 minutes after the first blood had been taken. They were also reminded that they would be asked about the types of food they had eaten during the last week. Participants were consented in batches, week by week. Consents were done on a Saturday morning, which was something new to our staff, but this was a time this younger group found more convenient. We used prior studies experience, which showed us that if participants were consented too far in advance from their first visit they were likely to forget to attend the clinic and therefore only consented five to six participants and gave them a booking. A challenge with this process was that when volunteers came to be consented brought their friends along who also wanted to be consented. We unfortunately had to turn volunteers away as our sample size was a fixed fifty. Some days; however, it did work to our advantage when someone who promised to come did not turn up the research team could then approach some of the new volunteers. The VCT testers and counsellors reported that more, younger people were coming to be tested for HIV hoping to join the study. This increased the workload for the clinic, which caused some tension, it was addressed by the research group offering to assist one day a week with VCT testing and counselling. The long-term outcome for the VCT testers was good as they were now reaching their set targets for routine testing, the study also include their age group they wanted to test. It was therefore a win–win situation for both groups and another relationship builder which would have positive spin off for other research projects being conducted at the clinic.

At the end of our summer clinic we had consented 52 participants, one participant did not come back as planned after being consented and was not exposed to any other research activity and the other, the research nurse was unable to bleed. For this reason, even though she/he had been consented and completed all the study documents an extra person had to be consented to achieve the target. Ethics was informed about the extra two

volunteers who were consented. The recruitment process and the actual summer clinic visits were completed in the allocated time of 6 weeks from the 01 February to the 05 March 2013.

All research activities excluding the full consenting process had to be repeated 4 months later after the Cape Town winter season. Staff suspecting that this would be a challenge with a group of young people who may in the interim have found work, enrolled at a college or as they were quite aware of in the Khayelitsha community, may have relocated. To decrease the length of time between visits the team decided that around June they would recall all participants one Saturday morning and discuss the study and remind them of their pending post winter season visit. This session very successful, of the 40 plus phone calls made 30 participants arrived on a cold Saturday morning in late June. They were given refreshments and their consent was re-discussed. Most of them clearly remembered the study, they openly discussed the study processes, and the study team reminded those who had forgotten some aspects of the study. They also promised to remind those participants they knew who did not attend that morning. The research nurse gave a talk about the pending protocol amendment which would require them to take 1 vitamin D tablet every week for 6 weeks and then return for their 25(OH) D levels to be done. This amendment was with ethics at the time and therefore the new consent document was not available for participants to read or take home with them. The research nurse then gave them appointments to return during the last week in July. From that response and the interactive morning, the team was positive they had a motivated group of study participants.

5.2.2 Staff Allocation and changes

When this study was launched the CIDRI group had an established research team working in the Khayelitsha area specifically at Site B health care centre. All staff were familiar with the Khayelitsha clinic environment. The team comprised of one research nurse and two CRW and a study co-ordinator who managed the study and supported the staff, but was required to do nursing duties when the nurse was away or busy with other departmental research activities. The research nurse leading this team had worked on many other observational studies in the CIDRI group including study two discussed above and was currently supporting other on-going

studies as required within the CIDRI group structure. The two Clinical Research Workers did the consents, the food diary questionnaires and the telephonic reminder calls, also assisted with other studies being conducted by the group. Staff were shared for this study as laboratory work could only be done on two specific days of the week, staff then organized their work to suit this requirement and assisted other studies on the other available working days. This was a novel system for the CIDRI group.

5.2.3 The impact of study outcomes linked to recruitment

Participants were reminded of their appointment the day before their visit by telephone, they promised to attend and be at the clinic around 0900. Often unfortunately this did not happen; on cold winter mornings, especially that these volunteers were not ill and had no “need” to come to the clinic. The team therefore had to call them again on the morning of the visit and hold off bleeding participants who were at the clinic so that blood samples could be done and arrive at the UCT laboratory within sixty minutes of the first sample being taken. Each clinic session therefore took much longer than we anticipated. As the research team members were shared with other studies this was rather disruptive, staff were required time to recall participants who were not arriving for their appointments. They also put a home visit system in place to actively recall or collect participants from college or places of work. After the study six-week window period for follow-up only thirty-three participants had returned. At this visit as per the protocol amendment they were invited to join next phase of the study. Everybody agreed, but one of the participants was pregnant and two tested HIV positive, which excluded them. The one pregnant participant was too anxious about her unplanned pregnancy and opted out of the study at this stage. Consents were completed with the thirty-one remaining participants; they were all given the prescribed vitamin D and given an appointment for six weeks later.

5.2.4 Retention

For the 6-week follow-up, staff followed the same procedure and started recalling participants the day before they were due to return. All 31 participants returned, but with much more effort from the staff. Participants were reminded on the day of their visit, staff called them if they had not turned up at the clinic by 0900. Our study

driver collected some of the participants at home, college or at the local train stations. Some had to be re-scheduled because they forgot to attend even though they had been reminded the day before. The laboratory had to run bloods every day even when only one or two participants attended. This was costly as same reagents were used in the laboratory in one participant or five participants returned.

Generally, the lost to follow-up rate was far higher than anticipated and in a staff debriefing, many of the team members attributed some of it to the protocol amendment which added another dimension to the study which participants had initially not signed up for. They felt that participants might have been apprehensive about taking vitamin D even though it was an approved supplement.

5.2.5 Descriptive summary of recruitment and retention trends

Table 4: Recruitment and retention throughout the study 3

Time from start of recruitment													
	-3	-2	-1	0	1	2	3	4	5	6	7	8	9
					Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct
Recruitment					46	5	no recruitment				Winter 33	26	5
			Protocol training		Screened and enrolled 51				Recall =30	Reconsent and follow-up X2			
Staff Hiring													
Lead investigator- non clinician	All lab work												
Project co-ordinator (nurse)			Clinician on clinic days only										
Study co-ordinator (nurse)			Already employed for other studies to oversee										
Research nurse			Already employed for other studies to lead recruitment										
4 CRW			Already employed for other studies to recruitment and recall										
Protocol Amendments													
Approved January 2013										Amendment			
										Extra time point 6 weeks of winter visit 6 weeks of weekly Vit D orally			

Initial recruitment went well but poor retention may have resulted from multiple issues, shared staffing, poorly timed protocol amendments, suspected impact of the weather, access to tertiary education, change in HIV status and anxiety about taking Vitamin D as prescribed.

5.3 Discussion

This study did not present any challenges from the outset, recruitment was easy; the “bring a buddy” system the CRWs adopted was very effective. Volunteers were young excited and interested in the research. It was noted that this excitement soon faded when the next activity occurred, which was finding a job, getting into college or being too cold to get up on a winter morning. These were some of the responses given when they were contacted per telephone. The study team felt that if they were able to consent volunteers who came back on the Saturday morning for the Vitamin D supplementation arm of the study there would have been a better response, however this cannot be confirmed. The poor follow-up made study team quite despondent and the small sample size of this study was something staff would usually achieve very easily. This study showed prolonged breaks between visits could prove a challenge.

6 Study 4

Defining mechanisms of immunopathology in TB-HIV co-infection and TB Immune reconstitution inflammatory syndrome (TB-IRIS)[1]

6.1 Introduction

The main purpose of the study was to determine what mechanisms drive tissue destruction in TB-HIV co-infection and TBIRIS.[1]- UCTHREC 516/2011

The experimental plan is comprised of two parts:

i) A cross-sectional clinical study to define MMP and NKT cell activity in HIV and TB

ii) A longitudinal clinical study to define MMP and NKT cell dynamics in TB-IRIS and allow proteomic analysis of blood from TB-IRIS patients compared to non-IRIS control patients.

Study population and clinical sites

The patients were enrolled to the clinical studies Part (i) and (ii) on presentation to clinical services in Khayelitsha Site B Health Care Facility Cape Town. As per approved protocol the recruitment was anticipated to occur at Ubuntu clinic, Site B, Khayelitsha. Additional patients if required would be recruited from Site B Youth Clinic and GF Jooste Hospital. Eligible patients were identified by a designated Xhosa and English-speaking research nurse already in employment with the group and had a good understanding of research processes and the clinic system.

Part (i): Cross-sectional clinical study

The team planned to recruit a cohort of patients in the following six study groups:

a) HIV negative asymptomatic controls (HIV-TB-)

b) HIV negative TB patients (HIV-TB+)

c) HIV negative respiratory symptomatic (HIV-RS+)

d) HIV positive asymptomatic controls (HIV+TB-)

e) HIV positive TB patients (HIV+TB+)

f) HIV positive respiratory symptomatic (HIV+RS+)

Part(ii): longitudinal study

Follow-up of HIV+ participants those who had abnormal blood results as hypothised in the protocol to observe if they would develop TBIRIS.

Inclusion criteria:

All patients presenting voluntarily to study sites, apart from those meeting exclusion criteria.

Exclusion criteria (all categories):

- asthma or chronic obstructive pulmonary disease (COPD)
- pneumothorax
- pregnancy
- unknown HIV status
- unable to give informed consent (cognitive deficit), language barrier
- mental illness
- prisoners
- on anti-retroviral therapy (ARVs)
- on tuberculosis therapy (>three dose)
- on steroid therapy
- suspected drug-resistant TB (based on contact history or existing gene-Xpert result)

6.2 Application of DAT

All data related to this study was captured on Microsoft Access and stored on the UCT network and is password protected. Access to this data base can only be gained via the data manger, who was given delegated authority by Professor Wilkinson. All requested data is sent in an excel format with only the variables requested. These

variables were reviewed to verify, date first participant was recruited, monthly recruitment totals, date last participant was recruited and dates of first and last follow-up. For the purposes of follow-up information, completed study visits were reviewed. This gave an indication of pace of recruitment and effectiveness of retention. Other information was sought from departmental human resource records and study regulatory files. Personal experiences of management of the study were also considered.

The protocol allocated twenty-four months to complete the clinical study activity, recruitment took seventeen months and retention eighteen months. Recruitment was consistent during this study with five months where twenty plus as achieved. In the month of August, a total of thirty-three achieved which ties in well with our experience of more patients presenting to the clinic with coughs and colds in the winter months giving recruiters a bigger pool of people to access. The study also had ten months of poor recruitment, this can be attributed to many things. Firstly, in month two a protocol amendment was made the lead investigator opted not to recruit, but to do more training. The second amendment was done at the end of October which is close to the normal dip in the clinic numbers due to the Christmas break. Therefore, the four recruited in November following the submission of the amendment was not directly linked to the amendment. The third amendment to enable recruitment after three doses of TB treatment had the desired effect and positively impacted the last few months of recruitment. The last few months of the study recruitment was purposefully slow and the lead investigator ensured that all the study groups had the correct number of participants and the recruit was very strategic to achieve those targets. Staff remained constant in this study and the disease of interest was not a challenge only the changing of the national health programme requirements for starting ARVs affected the rhythm of recruitment.

6.2.1 Recruitment as per protocol and protocol changes

Of all the studies being evaluated this study had the most significant protocol changes, which directly impacted recruitment, and follow-up as illustrated in Table 5.

Changes in protocol; approved 15 Nov 2011. The following changes were submitted.

- 10 June 2012, request for additional 10ml blood in Longitudinal follow-up, separate consent form for those entered directly into part ii and those who were first entered part i. An additional time point for longitudinal study
- 10 October 2012, additional site close to Site B, the local youth clinic with a view to increasing numbers. Change in CD4 count criteria from >one hundred cells/mm^3 to two hundred cells/mm^3.as fewer patients were presenting with lower CD4 counts. Removal of “have not received more than two weeks of anti-tuberculosis therapy at enrolment, with a view to increase recruitment.
- 21 January 2013, to enable recruitment of patients after < three doses of TB treatment, increasing the number of eligible patients as it would allow those who present to the clinic on a Friday to be recruited. Removal of steroid therapy as an exclusion criteria, as the number of patients who presented already on steroids would allow them to be evaluated as a separate group.

The plan was to recruit from the month of May in the second quarter of 2011 to the end of the second quarter 2012, a total of 13 months. Those recruited onto the longitudinal study would be followed up at two weeks, four weeks and twelve weeks, which would include first quarter of 2013. This ensured that those who had adverse events were followed up effectively. Forty participants would be recruited in each group resulting in a total of two hundred and forty participants which would give the study an eighty percent power answer the research question.

6.2.2 Staff Allocation and changes

As per budget this study would be run by a one research nurse supported by a study co-ordinator also a nurse who was employed in the 5^{th} month of recruitment also supported by two clinical research workers already working on other projects in the group. The study co-ordinator supported all ongoing studies and the nurse would be responsible for the study but assist on other ongoing studies. The lead investigator and PhD student would review all the eligible participants and embedded herself in the health care service, this process ensured a good understanding of the clinic process and served as a reminder for clinic staff to refer potential participants to the study team. Extensive training of two CRW and the research nurse had to take place to ensure continuity of

study processes and procedures and to ensure that participants were correctly identified and allocated to the correct study group. Although the lead investigator reviewed all participants the CRW identified potential eligible participants. Clinical Research Workers were trained to administer informed consent and to do mass waiting room information sessions.

6.2.3 The impact of study outcomes linked to recruitment

Recruitment remained steady, the lead investigator who was the clinician and the PhD student also needed perform all the laboratory work on all samples collected from the participants. This resulted in a limited number of patients who could be recruited per day. The policy of the department is also that all research nurses work interchangeably on all active studies, the lead investigator requested that she have a dedicated nurse, which worked well until the nurse was ill which slowed down all study activity, retention during the months of February and April where impacted due to the research nurse's ill health. Efforts to increase recruitment forced protocol changes as the health service changed its CD4 cell level for treatment with ARVs from two hundred to three hundred and fifty mm^3. This national programme change was made six months into the study and resulted in a dramatic decrease in recruitment in the following month. There also appeared to be a dip in recruitment when the longitudinal follow-up started, as all these participants had to be consented and volunteer for this arm of the study. The same amount of attention had to be paid to the consenting of these participants and recruitment for the cross-sectional study suffered. It dropped from thirty to fifteen, but fourteen participants were consented for the longitudinal arm that month. Recruiting for both arms of this study averaged at about thirty in total. This was affected by laboratory capacity, protocol change and ability of the staff to do two arms of the study simultaneously.

6.2.4 Retention

Of the two hundred and twenty-two participants recruited, forty-nine were eligible to join the longitudinal study, all were consented and agreed to join, they all joined at different times as this arm of the study required them to

start ARVs. All forty-nine attended their first three appointments, which required them to attend monthly. Latter visits were synchronized with the routine clinic visits. The ARV clinic had all patients newly started on ARVs return at fourteen days, twenty-eight days and then monthly for the first three months. It was therefore easy for them to present to the research staff as well. At this stage, stable patients where given the option to attend two to three monthly, the study team “lost” some of their participants who considered the research an extra visit. We put a system in place to remind them the day before, but many of them attended only on the day they were due to attend the clinic. The follow-up numbers slowly decreased although two hundred and six visits were made which was fifty percent of the planned follow-up visits. Each participant should have retuned for nine visits a total of four hundred and forty-four visits for all forty-nine participants. All required study information required for the follow up was easily retrieved from the clinic folders. Although no information was lost the follow-up was impacted by many factors, the clinic no longer requiring monthly follow-up, participants going to the Eastern cape over the November to February period and recruitment with simultaneous follow-up which is evident when the recruitment was winding down follow-ups were completed more effectively as reflected in Table 5.

Table 5: Recruitment and retention throughout study 4

Time from start of recruitment																												
	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
						May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	total
Recruitment						22	0	20	33	16	17	4	10	30	22	15	15	2	0	0	6	1	2	6	1			222
Retention										2	3	5	8	4	7	14	8	22	6	20	17	17	24	23	15	8	3	206
Protocol writing and planning				Protocol training			Screening (May 2012) and Enrolment (September 2012)																					
Staff hiring																												
Lead investigator																												
Study co-ordinator (nurse)									Hired to support all studies																			
Research nurse				N1 trained															N2 hired		N1 moved to		N2 left		N1 assisted			
CRW				3 CRW trained and worked interchangeably																								
Protocol Amendments																												
Approved November 2011							Amendment				Amendment			Amendment					Training									
							Longitudinal arm, one extra timepoint added				Addition of another site in			Enable recruitment even if after 3 doses of TB treatment in cross-sectional study					Lead investigator away recruitment paused, only longitudinal follow-ups done									
							Increase of blood volume by 10ml at each longitudinal visit				Increase of CD4 count from 100-200			Removal of "on steriod therapy" in longitudinal														
							Increase of sample size of longitudinal arm from 64-100				Removal of have not received more than 2 weeks anti-tuberculosis																	
							Inclusion of genetic studies, additional consent																						
											Inclusion of GeneXpert results in case definition																	

Recruitment was done in seventeen months over a twenty-month period with three months of no recruitment due to the academic needs of the PhD clinician leading the study and staff training. This did not disrupt the momentum of the study as follow ups continued during this period. None of the protocol amendments negatively impacted the recruitment. The pause in recruitment for training with regards to the processes in the longitudinal study proved to be very effective as follow-ups improved. This study also used the contact tracing system. They would contact the participants by the telephone and after three failed attempts to make telephonic contact the team would do a home visit to remind the participant of their study visit. This was a process that other on-going studies in the group were implementing effectively and was therefore used in this study as well.

6.3 Discussion

In the longitudinal arm the study was very effective while the participants could synchronise their visits with routine clinic visits to collect their newly prescribed ARVs, but as the stable patients were referred to community groups and 3 monthly follow-ups the study then struggled to get participants to come back for what they considered an extra visit. Research nurses assigned to this study were challenged by not being able to do follow-ups as per booking. On occasion, they would randomly get a participant to come to attend a study visit, but encountered participants blood samples could not be processed in the laboratory as laboratory assays needed to be prepared twenty-four hours in advance to process the samples. Participants then needed to return on a specific day, which was not always possible. The CRWs on the other hand developed a good rapport with the participants; which positively impacted their follow-up.

Having fixed timelines and a plan for recruitment in place was an asset to this study. The challenge on the other hand was having two study designs in the study, the staff found this difficult to manage sometimes, but having a lead investigator so personally committed to the study and supportive to the staff helped them get through these times. The lead investigator requested one nurse work on this study and that worked well. All study outcomes were achieved even those there was a significant lost to follow-up, clinic folders were reviewed and al required information was collected. The diseases required in this study (HIV/TB) were easy to access as the study was based at a TB/HIV clinic.

7 Conclusion

Without the ability to recruit and retain study participants and complete research, changes in policy and publications would not be possible. Each of these studies have been published in journals, like the Lancet, Nature and Science Magazine. One of these studies changed provincial policy; another offered better insight to latent TB and the last is now being linked to other studies that are doing work with TB and vitamin D as a protective factor against TB.

It is evident that study all team members are the recruitmentologist; skills, personality, ability and understanding of the processes is what separates the good ones from the great ones. Skilled[4] recruiters acknowledge the science they understand the impact non-recruitment has on a protocol. As per study three in this review the age of the participants did not negatively impact the ability to recruit, but did the ability to retain. Shapiro[6] identifies that recruiters must be aware of age and climate as they are important factors to acknowledge and work with. The study recruited a group who were mobile, seeking access tertiary education and employment. Additional visits added on subsequently disrupted motivation to remain in the study, Lisa K. Berger, *et al* [8]. Yet other long term follow-up as in study one for more than two years did not have the same effect. The latter group were patients seeking health care before they became study participants. The pragmatic approach that was used during this study positively impacted the recruitment as retention. This was effectively used in the community of Khayelitsha with no extra costs. Consideration must also be given to those who are healthy volunteers as in study three or “patients” seeking care as in the other three studies.

As discussed by Galbreath, A. D. *et al* [7] protocols must include an effective marketing strategy, which all the studies reviewed in this paper lacked. Studies relied solely on the memory and skill of the recruiter. Lisa K. Berger, *et al* [8] suggests that appropriate questions are asked at screening; which include ability to get time off work, attendance of college, job seeking and plans

to relocate. More money could be spent on screening which would result in a saving during retention and extending recruiting due to in adequate sample size. Other simple tools like roles and responsibilities charts for staff and participants could be designed and displayed; which could be referred to at visits this would encourage conversation where reasons for missed visits for that group can be addressed. Using technology available as suggested by Schneider, K.E.w.J.C [10]; all studies reviewed only used cell phone numbers and they were all only used to make phone calls, other technologies have developed and could be used, social platforms should be investigated. Emails as an option have not yet been explored, yet this is used by all local retailers, where a large majority of the volunteers in these studies purchase goods. Schneider, K.E.w.J.C [10]suggests a finder's fee, which we used in study two and three with limited success, participants who were already on studies within the group where encouraged to refer potential participants to the research group. If any of the participants were successfully enrolled the "finder" was given a cash incentive. This was done without compromising the integrity of the study, and confidentiality was always strictly maintained.

The "finders" were not aware which study the volunteer they brought to the clinic was enrolled into. Another shortcoming of the studies reviewed was the lack of retention plan in the protocols Schneider, K.E.w.J.C [10] insists that this become the norm. Incentives for participants who achieve milestones should be implemented. Offering small incentives for example, mugs for completing first 5 follow-up visits, sending thank notes and birthday wishes via social platform should be encouraged. Contacting participants about non-study events like World TB day, Woman's' day activities at the clinic, shows interest in the participants' health and well-being and not only as the "next follow-up visit".

Although this review showed many potential areas of improvement, its successes proves that the recruitmentologist employed by the group, working within the parameters of study design as per

the protocol when recruiting the appropriate participants are very important cogs in the wheels in this recruitment process. The group's staffing is an area where matters should be improved, because short term contracts due to instability of funding, does not offer economic security to staff. This results in nurses looking for more stable work, which has not given the group the time to develop into a stable research group. Although the group sometimes struggled from a human resources perspective only in study four was recruitment interrupted, which was due to the availability of the lead investigator and not nurses and clinical research workers inability to recruit. The largest of these studies; study one which was the first of its size to be conducted in the group allowed the group to make adaptations on how we recruit staff to cost effectively impact the recruitment process, while these processes are undocumented, they are rather "lessons learnt." We could have been even more effective as a group in our ability to recruit if we documented recruitment plans for each study as we rolled them out for each study. Having a visual plan for recruitment with each protocol should become standard practice.

Although the group managed to publish papers with study three more information could have been collected if all follow-ups visits were successfully completed. Data collected during the screening stage, proved vital with regards to the publication. In study one, the outcome impacted local government policy and was the first study of its kind to be done in that particular population.

The diseases of TB and HIV have proved not to be a deterrent in the ability to recruit, but personal experience within this community gave staff the insight required to be effective recruitmentologist. The active campaigning of NGOs and human rights groups with regard to health and the health care offered by researchers working in this community also continue to positively impact research and recruitment in the community.

8 Discussion and Recommendations

These four studies although they had very different study designs, they all had similar challenges. Recruitment was not impacted by specific study design; retention was affected more by clinic operational changes. Recruitment was done more effectively when the clinic was running a full capacity and not over the November to January period when the clinic numbers were low. All study teams had to be prepared to change recruitment and retention tactics to suit the study needs and synchronise their activity to that of the clinic and the mobile community. Study three in this paper had the poorest outcome with regard to retention with the smallest sample size. This study had limiting factors on being was the age group, the study required volunteers between the ages of eighteen and twenty-five years and had a long break between the three visits. This was also a more mobile group who lost interest in the study or entered the job market. More research around recruitment of this age group is recommended in Khayelitsha as this was not part of this review. Study designs are used to answer the question and in none of these studies did the design negatively impact the ability to recruit, although the follow-up was impacted as described above. Although the study may not have required the follow-up done in the way it was, a folder review still allowed the study staff to collect the required information, therefore follow-up could have been done in the form of a folder review.

Staff members in this research group needed to be flexible and work across all studies as all these studies were individually funded for short periods of time. To ensure job security staff had to work on one study which was ending while another one was starting up, which could result in lack of focus for either study. On the other hand, the ability to move from one study to the other would keep the larger team well trained and ready to accept any new studies conducted by the group. It will also ensure that during periods of staff illness, planned and unplanned leave, recruitment and retention can continue. Staff also gained confidence when working on different studies, with different requirements and different lead investigators. Nurses need to have full

understanding of TB, HIV and all health promotion programmes in the clinic and community to effectively work without disrupting systems. The team must have the ability to work within the clinic and compliment non-research staff. Although this review could not consistently link any negative impact on recruitment to the protocol amendments, the study teams were always anxious about these amendments. The lead investigators managed these amendments well, by ensuring that other study activity could continue and kept the participants and the study teams informed of the amendments. Only the study with the seasonal follow-up did not manage to succeed with this approach, although the research team attempted to keep participants interested it was not effective. The study team discussed this after the study had closed and suggested the lead investigator that monthly telephone calls could have been budgeted for; as regular contact with this young group of participants may have positively impacted retention. It was evident that all the recruitment and retention styles and tactics must be visited throughout the study and not be too rigid, if one system does not work and new approach must be considered.

9 Annexure 1

Data Abstraction Tool (DAT)

1. Study Tittle
2. Data base format
   2.1. Access
   2.2. File maker
   2.3. Excel
   2.4. Other_____
3. Date reviewed_____
4. Reviewed by_____
5. Information collected
   5.1. Recruitment as per protocol and protocol changes (descriptive: to include study design and protocol changes related to recruitment)
      5.1.1. Record of recruitment targets
      5.1.2. Date first and last participant recruitment
      5.1.3. Date recruitment started
      5.1.4. Monthly recruitment totals
      5.1.5. Date first and last participant follow-up
      5.1.6. Date protocol amendments made which possibly affected recruitment and or retention were made.
   5.2. Staff allocation and changes
   5.3. The impact of study outcomes linked to recruitment (descriptive)
   5.4. Retention
   5.5. Trends of increase or decrease in recruitment (tabulated)

10 References

1. Wilkinson, R.J., *University of Cape Town Human Research Ethics; Four Approved Protocols*. 012/2007, 013/2007, 516/2011, 003/2013.

2. Epstein, S., *The rise of "Recruitmentology": Clinical Research, Racial Knowledge, and the Politics of Inclusion and Difference. .* Social Studies of Science, Race, Genomics and Biomedicine 2008. **Volume 38**(No 5): p. 801-832

3. Government, W.C., *Clinic List*. 2014, This project is an initiative of the Western Cape Government.

4. Ury, R.F.a.W., *Getting to yes*. 2012, Random House Business Books.

5. Tappen, R.M., in *Advanced Nursing Research from Theory to Practice*. 2011, Jones and Bartlett Learning. : Printed in the USA.

6. Shapiro, A., *Study Participants Retention in Clinical Trials.* Retina Today, September 2013.

7. Autumn Dawn Galbreath, B.S., Pamela Wood, Emma Forkner, Jay I Peters, *Cumulative recruitment experience in two large single-center randomized, controlled clinical trials.* Contemporary Clinical Trials, 2008. **Volume 29**(Issue 3): p. Pages 335-342.

8. Berger, L.K., A.L. Begun, and L.L. Otto- Salaj, *Participant recruitment in intervention research: scientific integrity and cost- effective strategies.* International Journal of Social Research Methodology, 2009. **12**(1): p. 79-92.

9. *ICH guidelines Declaration of Helsinki*. 2012, Johns Hopkins University. Centre for Immunization Research.

10. Schneider, K.E.w.J.C., *The CRA's Guide to Monitoring Clinical Research*. 2011: 3rd Edition Centre Watch.

11. *City of Cape Town – 2011 Census – Khayelitsha Health District*, in *City of Cape Town 2011 Census data supplied by Statistics South Africa*. 2013, Complied by Strategic Development Information and GIS Department (SDI&GIS).

12. *Isoniazid plus HAART to prevent tuberculosis in HIV – infected persons*, U.T.C. Town, Editor. 2007: UCT Human Ethics Committee