

**EXPLORING THE  
ANCILLARY-CARE EXPERIENCES  
OF STAKEHOLDERS  
IN SOUTH AFRICAN  
HIV VACCINE TRIALS**

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# DECLARATION

**Submitted in fulfillment of the requirements of the degree of Doctor of Philosophy in the Graduate Program of the School of Applied Human Sciences, College of Humanities, University of KwaZulu-Natal, Pietermaritzburg, South Africa**

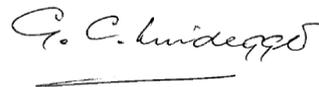
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Ms Catherine Slack

6 February 2015



Professor Graham Lindegger

6 February 2015

# ABSTRACT

A controversial debate in research ethics comprises the responsibilities of sponsors and researchers to address participants' medical needs in low-resource settings when this would not service the scientific objectives of the research, nor keep participants safe – their so-called 'ancillary-care' responsibilities – particularly when responses might be costly or demanding. The ancillary-care debate partially emerged out of the field of HIV vaccine trials. There has been surprisingly little effort to systematically explore the practices and perspectives of researchers (and other key role-players) regarding ancillary care in such trials. This qualitative study aimed to explore the experiences of key stakeholders involved in HIV vaccine trials in South Africa, specifically: their practices, how such practices are made sense of or understood, and contemporary concerns and complexities. It was funded by the Wellcome Trust Biomedical Ethics Program (087429/Z/08/Z). Semi-structured interviews were conducted with representatives of the coordinating network as well as Research Ethics Committees, Community Advisory Boards and research staff at five sites in the country implementing two HIV vaccine trial protocols. Key documents were obtained, including protocols, informed consent forms and supporting documentation. The study obtained necessary ethical approvals (UKZN BREC BE 241/09) and written consent was provided for study participation. Data was analyzed using Thematic Analysis to develop themes that captured meanings attributed by interviewees to their practices and experiences. Five master themes were developed namely *Reciprocating, Engaging, Benefitting*; as well as *Reconciling, Privileging, Line-drawing, and Partnering*. These master themes, and sub-themes, are discussed in terms of the ancillary-care literature. The study sets out implications of stakeholders' ancillary-care experiences for leading accounts of ancillary care, as well as for current ethical guidelines. Recommendations are made to refine guidance so it is more responsive to the concerns and complexities experienced by stakeholders in the field. Recommendations are made to strengthen the practices of core stakeholders. It is hoped that through refined guidance and strengthened practices this study can contribute to the ethical rigor with which such trials are implemented.

Key words: HIV prevention trials, HIV vaccine trials, ethics, research ethics, ancillary care, access to treatment, standard of care, empirical data.

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# DEDICATION

To Doug and Daniel

# TABLE OF CONTENTS

<b>ABSTRACT</b>		i
<b>ACKNOWLEDGMENTS</b>		ii
<b>DEDICATION</b>		iii
<b>TABLE OF CONTENTS</b>		iv
<b>CHAPTER ONE</b>	<b>INTRODUCTION</b>	<b>1</b>
<b>1.1</b>	<b>BACKGROUND</b>	<b>1</b>
<b>1.2</b>	<b>STUDY AIMS AND APPROACH</b>	<b>4</b>
<b>1.3</b>	<b>STUDY OUTLINE</b>	<b>5</b>
<b>CHAPTER TWO</b>	<b>LITERATURE REVIEW</b>	<b>6</b>
<b>2.1</b>	<b>INTRODUCTION</b>	<b>6</b>
2.1.1	The HIV epidemic and responses internationally	6
2.1.2	The HIV epidemic and responses in South Africa	8
2.1.3	Health research with human participants	13
2.1.4	Health research with human participants in South Africa	15
<b>2.2</b>	<b>HIV VACCINE TRIALS</b>	<b>16</b>
2.2.1	Aims, phases and stakeholders in HIV vaccine trials	16
2.2.2	HIV vaccine trials in South Africa	20
<b>2.3</b>	<b>THE DEBATE ABOUT CARE IN HIV VACCINE TRIALS</b>	<b>21</b>
2.3.1	Introduction	21
2.3.2	Standards of care	23
2.3.3	Ethical principles	27
2.3.4	Models of ancillary care	36
2.3.4.1	The partial entrustment account of ancillary care	37
2.3.4.2	The whole person account of ancillary care	42

2.3.4.3	The Four P's account of ancillary care	45
2.3.5	Community engagement	46
2.3.6	Summary of the access to care debate	49
<b>2.4</b>	<b>RECOMMENDATIONS IN ETHICAL GUIDELINES</b>	<b>50</b>
2.4.1	Guidance not specific to South African HIV vaccine trials	50
2.4.2	Guidance specific to South African HIV vaccine trials	53
2.4.2.1	Guideline recommendations for participants	54
2.4.2.2	Guideline recommendations for non-participants	56
2.4.2.3	Guideline recommendations for engagement	57
2.4.3	Summary of ethical guidelines	61
<b>2.5</b>	<b>PRIOR EMPIRICAL EXPLORATIONS OF CARE</b>	<b>62</b>
2.5.1	Summary of empirical explorations	72
<b>2.6</b>	<b>SUMMARY OF THE LITERATURE REVIEW</b>	<b>72</b>
<b>CHAPTER THREE</b>	<b>STUDY AIMS AND METHODOLOGY</b>	<b>74</b>
<b>3.1</b>	<b>STUDY AIMS</b>	<b>74</b>
<b>3.2</b>	<b>STUDY APPROACH</b>	<b>75</b>
3.2.1	A qualitative study	75
3.2.2	An interpretivist framework	75
<b>3.3</b>	<b>STUDY METHODOLOGY</b>	<b>76</b>
3.3.1	Background and reflexivity	76
3.3.2	Preparing the ground and addressing ethical components	80
3.3.3	Developing a sampling strategy for interviewees	81
3.3.4	Accessing interviewees	82
3.3.5	Designing a semi-structured interview schedule	85
3.3.6	Ensuring informed consent	89
3.3.7	Conducting interviews	90
3.3.8	Sample characteristics	92
3.3.9	Coding and analysis	94
3.3.9.1	Step 1: Reading and re-reading the interview transcripts	96

3.3.9.2	Step 2: Developing first level codes	97
3.3.9.3	Step 3: Listing first level codes	98
3.3.9.4	Step 4: Sorting first level codes into code-clusters (sub-themes)	98
3.3.9.5	Step 5: Developing theme tables for individual interviews	99
3.3.9.6	Step 6: Developing theme tables across interviews	100
3.3.9.7	Step 7: Coding documents	100
3.3.9.8	Step 8: Continuing coding of subsequent interviews	101
3.3.9.9	Step 9: Continuing to structure codes into subthemes and master themes	101
3.3.9.10	Step 10: Naming master themes	102
3.3.9.11	Step 11: Writing master themes into a narrative	103
3.3.9.12	Step 12: Considering 'saturation'	104
3.3.9.13	Step 13: Checking if themes were internally consistent and distinct	104
3.3.9.14	Step 14: Interpreting master themes	105
<b>3.4</b>	<b>STUDY QUALITY</b>	<b>105</b>
3.4.1	Including a reflexive account	105
3.4.2	Making use of triangulation	106
3.4.3	Making use of more than one researcher	107
3.4.4	Leaving an audit trail	108
3.4.5	Aiming for a rich detailed account	109
3.4.6	Including verbatim extracts	109
3.4.7	Looking for dis-confirmatory evidence	110
3.4.8	Soliciting member reflections	111
3.4.9	Considering implications beyond the sample	112
<b>3.5</b>	<b>STUDY LIMITATIONS</b>	<b>112</b>
<b>CHAPTER FOUR</b>	<b>RESULTS</b>	<b>114</b>
<b>4.1</b>	<b>RECIPROCATING, ENGAGING, BENEFITTING</b>	
	<i>'...these people stand up and be counted...'</i>	114
<b>4.2</b>	<b>RECONCILING: '...we are providing a better service...'</b>	119
<b>4.3</b>	<b>PRIVILEGING: '...should standard of care in our prevention centres be different..?'</b>	125

4.4	<b>LINE-DRAWING:</b> <i>'...people must be reasonable you know...'</i>	132
4.5	<b>PARTNERING:</b> <i>'...the ball is not only in our hands...'</i>	139
4.6	<b>SUMMARY OF RESULTS</b>	150
<b>CHAPTER FIVE</b>	<b>DISCUSSION</b>	<b>153</b>
5.1	<b>RECIPROCATING, ENGAGING, BENEFITTING</b>	153
5.2	<b>RECONCILING</b>	161
5.3	<b>PRIVILEGING</b>	165
5.4	<b>LINE-DRAWING</b>	173
5.5	<b>PARTNERING</b>	181
5.5.1	Site-staff and participant interactions	182
5.5.2	Site-staff and service-provider interactions	182
5.5.3	Site-staff and network interactions	184
5.5.4	Site-staff and community representative interactions	185
5.5.5	Site-staff and REC interactions	189
5.6	<b>SUMMARY OF DISCUSSION</b>	191
<b>CHAPTER SIX</b>	<b>CONCLUSIONS AND RECOMMENDATIONS</b>	<b>194</b>
6.1	<b>CONCLUSIONS</b>	194
6.1.1	Stakeholder practices and perspectives	194
6.1.2	Stakeholder concerns and complexities	195
6.1.3	Implications for ethical models and ethical guidelines	196
6.1.3.1	Implications for ethical models of ancillary care	196
6.1.3.2	Implications for ethical guidelines	200
6.2	<b>RECOMMENDATIONS</b>	204
6.2.1	Recommendations for ethical models and ethical guidelines	205
6.2.1.1	Recommendations for models of ancillary care	205
6.2.1.2	Recommendations for ethical guidelines	207
6.2.2	Recommendations for practices	212

6.2.2.1	Recommendations for researcher and network practices	212
6.2.2.2	Recommendations for REC practices	214
6.2.2.3	Recommendations for CAB practices	215
6.2.2.4	Inter-stakeholder recommendations	215
6.2.3	Recommendations for additional research	216
<b>6.3</b>	<b>FINAL REMARKS</b>	<b>220</b>
<b>REFERENCES</b>		<b>222</b>
<b>APPENDICES</b>		<b>256</b>
Appendix 1	Summary of recommendations in ethical guidelines	256
Appendix 2	Letter of request for documents	260
Appendix 3	Informed consent form	262
Appendix 4	Summary of first-level codes clustered in sub-themes and master themes	267
<b>LIST OF TABLES</b>		
Table 1	Summary of study participant numbers per stakeholder group	93
Table 2	Summary of protocol descriptions regarding care steps	147
Table 3	Summary of consent form descriptions regarding care steps	149

# CHAPTER ONE

## INTRODUCTION

### 1.1 BACKGROUND

Many countries around the world face the health threat and burden posed by Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) (Global Enterprise, 2012). Global responses to the HIV epidemic include efforts to provide antiretroviral therapy (ART) to infected persons who need it, as well as to develop strategies to prevent HIV acquisition in the first place. Prevention efforts aim to scale-up proven HIV interventions while simultaneously researching innovative new prevention tools (Warren & Bass, 2013). Research into new HIV prevention tools includes the testing of experimental HIV vaccines, and HIV vaccine trials involving human participants have taken place in numerous countries around the world, including South Africa.

HIV vaccine trials enrol participants who undergo numerous trial procedures including assessments of their HIV and health status, among other procedures. It has long been recognized that such trials will be ethically complex, in part because such trials involve actors from high-income settings working in collaboration with those from more resource-constrained settings (WHO/UNAIDS, 2004) – the latter often but not exclusively the location of such trials. Also, participants may have multiple vulnerabilities, such as inadequate education, impoverishment or marginalization that may compromise their decision-making about trial enrolment or increase their risk of trial-related harms such as stigma (UNAIDS, 2000a; UNAIDS 2000b). It was recognized early that the conduct of HIV vaccine trials would require dedicated attention to the ethical components - to ensure that the rights and welfare of human participants were protected and promoted while such persons contributed to the social good of developing knowledge and interventions to prevent HIV (Guenter, Esparza & Macklin, 2000; WHO/UNAIDS, 2004).

South Africa faces an especially high burden of HIV and the South African government has endorsed research into biomedical HIV prevention tools, including HIV vaccines (SANAC, 2007; SANAC, 2012). In South Africa, HIV vaccine development and testing with human participants has been coordinated by the South African AIDS Vaccine Initiative (SAAVI). Since 2000 I have worked as the project coordinator at the HIV AIDS Vaccines Ethics Group (HAVEG) which has been funded by SAAVI (and others) to undertake research and resource-development to help address ethico-legal complexities in HIV vaccine trials in South Africa.

One controversial ethical issue in HIV vaccine trials comprises the responsibilities of sponsors and researchers to respond to participants' medical needs, where such responses are not required for the scientific success nor safety of such trials, where local care alternatives for participants' needs may be inadequate and where responses may be costly or demanding to implement – including ensuring access to ART for participants residing in settings where ART access may be unreliable (Richardson, 2007). Responses to medical needs that fall outside the familiar rationales of science or safety have come to be termed 'ancillary-care' responses or extra-scientific responses that are expressly about 'positive helping performances' (Richardson, 2012c, p. 206). HIV constitutes a life-long, debilitating terminal illness if left untreated and ART is a relatively expensive and complex treatment, therefore the ancillary-care debate in HIV vaccine trials initially focussed on participants' access to ART for HIV infection. In the South African setting, this issue was starkly accentuated by delayed roll-out of ART in the public sector linked to a denialist government response (cf. Venter, 2013). More recently the debate has expanded to examine sponsor-investigator obligations to respond to participants' multiple health threats, such as other Sexually Transmitted Infections (STIs), unintended pregnancies or other health conditions, in settings where service-delivery may be constrained or inadequate (MacQueen & May, 2008).

The debate about researchers' ancillary-care responsibilities in HIV vaccine trials has had many facets. In addition to debate about the *needs* that researchers should focus on – HIV or medical needs more broadly (MacQueen & May, 2008) - there has also been debate about the *party* researchers should focus their attention on, such as participants enrolled in trials, or persons who present for screening but may not be enrolled, or even the broader community (Shapiro & Benatar, 2005). There has been debate about the *responses* that researchers

should be implementing particularly when the responses will be costly and resource-intensive (Participants, 2008). There has been debate about the most rigorous *justification* underpinning researcher's care responsibilities (Benatar & Singer, 2000; Macklin, 2006a; MacQueen & May, 2008; Richardson, 2007; Stobie & Slack, 2010; Schüklenk & Ashcroft, 2000). There has also been debate about how to involve stakeholders such as the participating community in care-related issues (Tarantola, Macklin, Reed, Osmanov, Stobie, & Hankins, 2007; Weijer & LeBlanc, 2006). An expanded set of ethical guidelines make recommendations about these issues (SA MRC, 2003; UNAIDS/WHO, 2007; 2012; UNAIDS/AVAC, 2011) to help guide the actions of key stakeholders and to provide them with ethical direction. Recent ethical frameworks have also been advanced (Dickert & Wendler, 2009; Richardson & Belsky, 2004; Richardson, 2007). These ethical guidelines and models propose various ethical rationales grounding researchers' responsibilities, in addition to making recommendations for researcher conduct.

Empirical data about ancillary-care practices have been systematically collected for non-vaccine prevention trials (cf. Heise, Shapiro & West Slevin, 2008; MacQueen & May, 2008) but systematic exploration in HIV vaccine trials has been limited (Macklin, 2009). As part of HAVEG, I was involved in securing a grant from the Wellcome Trust Biomedical Ethics Program to conduct an empirical exploration of the care practices of stakeholders (alongside HIV prevention practices) to compare these to recommendations in ethical guidelines. As part of the literature review for that project, it became clear that previous empirical studies have focused more on practices to address needs (cf. Ngongo et al., 2012) with fewer efforts to characterize in detail how HIV vaccine stakeholders themselves understand, frame or make sense of ancillary-care responsibilities, and the challenges and complexities they perceive as especially pressing. Previous empirical work has also utilized empirical data to inform helpful recommendations for practices, with less attention to utilising empirical data to inform a critical reflection on ethical guidance, for example, by documenting concerns and complexities for which ethical guidance should offer more direction. After the grant was awarded I sought additional approvals to complement the original project with a more detailed exploration towards a PhD dissertation.

## 1.2 STUDY AIMS AND APPROACH

In this study, I aim to explore the experiences of multiple stakeholders impacting on ancillary care in South African HIV vaccine trials, in order to facilitate a critical reflection on ethical guidance for ancillary care. More specifically, I aim:

1. To explore stakeholder practices and how stakeholders perceive, understand or make sense of ancillary-care practices in HIV vaccine trials
2. To explore stakeholder concerns and complexities regarding ancillary care in HIV vaccine trials; and
3. To explore the implications of stakeholders' ancillary-care experiences for current ethical models and ethical guidelines.

To provide a rich and detailed account of ancillary care, I adopted a qualitative approach in this study because it allows researchers to study issues in 'depth, openness and detail' (Durrheim, 2006, p. 47). Empirical findings cannot in themselves settle the considerable debate about ancillary-care responsibilities (cf. Grady et al., 2008) but empirical findings might help to refine ethical guidance by revealing concerns and complexities for which guidance should be more responsive (Draper & Ives, 2007) thereby helping to ensure more attuned guidance for vaccine stakeholders.

This study hopes to make a specific contribution to HIV vaccine trials by strengthening the ethical rigor with which ancillary-care issues are addressed - through more responsive guidance and improved practices. More generally this study hopes to make some contribution to the field of health research with human participants more broadly - which is concerned with promoting participants' rights and welfare while they take part in research that aims to develop knowledge and interventions to promote health (Emanuel, Wendler & Grady, 2000; Emanuel, Crouch, Arras, Moreno & Grady, 2003; Emanuel, Crouch, Grady, Lie, Miller & Wendler, 2008). While much of health research ethics is underpinned by conceptual analysis that uses the methods of philosophy to clarify concepts, ground ethical positions and make ethical judgments (Emanuel, 2002a), there is increasing recognition that conducting empirical research may play a role in strengthening ethical guidance by for example

identifying new problems or even finding nuances in familiar problems for which ethical guidance should be more responsive (Draper & Ives, 2007).

### 1.3 STUDY OUTLINE

The thesis takes the following form: in the chapter that follows (chapter two) the context for HIV vaccine trials is briefly reviewed, the debate about ancillary care is reviewed in detail, as are leading models of ancillary care, current ethical guidelines and previous empirical explorations. The following chapter (chapter three) describes the aims and methodology of the study including strategies to enhance quality. The subsequent chapter (chapter four) sets out the results in the form of master themes and their constituent sub-themes. The next chapter (chapter five) discusses these themes in terms of the literature on ancillary care. The final chapter (chapter six) sets out the main conclusions of the study against the specific aims, including the implications of the empirical findings for leading ethical models and current ethical guidelines. It also makes a series of recommendations for how distinct trial stakeholders might strengthen their ancillary-care practices.

# CHAPTER TWO

## LITERATURE REVIEW

This chapter, firstly, introduces the context for the issue being explored in this thesis, namely ancillary care in HIV vaccine trials, by reviewing the need for HIV vaccines, despite treatment and prevention successes, and by reviewing the need for ethical rigor in research with human participants. Secondly, this chapter describes HIV vaccine trials and their ethical complexity. Thirdly, it reviews the specific debate about the responsibilities of researchers and sponsors towards care needs identified in HIV vaccine trials, including debate about what grounds these responsibilities, the needs that should be attended to, the parties most deserving of care, the responses that should be implemented, the role of the participating community, and leading models of ancillary care. Fourthly, it reviews recommendations in current ethical guidelines. Finally it briefly reviews the debate about the contribution empirical data can make to ethical debates and reviews previous empirical explorations of care.

### 2.1 INTRODUCTION

#### 2.1.1 THE HIV EPIDEMIC AND RESPONSES INTERNATIONALLY

HIV/AIDS has resulted in 25 million deaths since 1981, and every year there are 2.5 million new infections in the world (Global Enterprise, 2012). HIV/AIDS has been identified as the most serious global health challenge of our time, accompanied by an epidemic of stigma and discrimination (UNAIDS, 2011). One of the most notable achievements in the HIV response has been the dramatic expansion in ART-access (UNAIDS, 2011). In the late 1990's 'triple' ART changed AIDS from a fatal condition to a manageable chronic disease in those settings that could afford the approximately 20,000 USD a year it cost to treat every patient (Abdool Karim, 2011). Due to its high cost, ART remained largely unavailable in low to middle income countries between 1996 and 2000 where small-scale programs providing symptomatic and palliative care were the only treatment options (UNAIDS, 2011). Dramatic improvements in

the scale-up of ART in low-resource settings occurred between 2001 and 2010 after sustained concerted international protest, lowered ART costs from generic producers and pharmaceutical companies, large-scale international support and the launch of the WHO '3 by 5' campaign in 2003 to deliver ART to three million people by end-2005 (Bongaarts, 2013; Merson, Malley, Serwadda & Apisuk, 2008; UNAIDS, 2011; UNAIDS, 2013). Through initiatives such the Global Fund to Fight AIDS, TB and Malaria (GFATM) established in 2001, and the US President's Emergency Plan for AIDS Relief (PEPFAR) established in 2003 'the impossible' became possible in resource-constrained settings (Abdool Karim & Bayer, 2013, p. ii; Abdool Karim, 2011). In fact, as of December 2012, an estimated 9.7 million people were on ART in low- to - middle-income countries (AVAC/AMFAR, 2013). PEPFAR funding to low-resource countries contributed not only to ART provision but also to other products needed to manage opportunistic infections, and to building infrastructure and personnel expertise (Cooper & Mills, 2009).

Despite significant advances in ART access it has been estimated that globally of every five persons needing ART only two receive it (Global Enterprise, 2012). It has also been noted that late diagnosis, sub-optimal linkage to care, and insufficient adherence to ART still represent key barriers to optimal treatment outcomes even in high-income settings (Gardner, McLess, Steiner, del Rio & Burman, 2011). Commentators have also observed that 'full and continuous access to ART could be threatened by weak economies' even in resource-rich regions (Volberding & Deeks, 2010, p. 53).

It is widely accepted that significant advances in HIV treatment will not necessarily diminish the burden of HIV infection (El-Sadr, Serwadda, Sista & Cohen, 2013). Research has demonstrated that when HIV-infected persons receive ART that suppresses their viral load this can prevent the sexual transmission of HIV to others (Abdool Karim, 2011) which expands the 'individual-level survival benefit of antiretroviral treatment to a dyadic level prevention benefit' (Abdool Karim & Bayer, 2013, p. ii). However, it has been asserted that 'we cannot treat our way out of this pandemic' (Merson et al., 2008, p. 485) and UNAIDS (2011) estimates that for every three persons receiving ART in low to middle income countries five more persons become HIV-infected.

It has been argued that concerted efforts must take place to implement or scale-up existing HIV prevention tools (El-Sadr et al., 2013; Warren & Bass, 2013). Optimal HIV prevention strategies will likely require combination prevention where a package of prevention modalities is tailored or customized to particular risk factors in particular settings and sub-populations (Abdool Karim, 2011; El-Sadr et al., 2013; Padian et al., 2011a; Padian et al., 2011b; Rotheram-Borus, Swendeman & Chovnick, 2009; Warren & Bass, 2013). A combination prevention approach also rests on the view that any one HIV prevention modality is unlikely in and of itself to be 100% effective but rather partially effective in preventing HIV (Rotheram-Borus et al., 2009).

Alongside the scale-up of known HIV prevention tools, there is a need for innovative new HIV prevention strategies that can address the needs of particular settings and sub-groups. Research into innovative new prevention modalities has yielded optimistic results in recent years. In addition to research showing that sexual transmission of HIV in heterosexual discordant couples can be prevented when the infected sexual partner is on ART, research has shown the HIV prevention efficacy of voluntary medical circumcision for men, vaginal tenofovir gel (microbicides) for women, and oral antiretrovirals (ARVs) for men who have sex with men, discordant couples, and heterosexual women – so called pre-exposure prophylaxis (El-Sadr et al., 2013). However, the Global Enterprise (2012) has argued that preventive HIV vaccines represent the best hope for long-term control of the HIV epidemic (Global Enterprise, 2012) in part because their use is less dependent on behavioural compliance than many other biomedical modalities currently being explored, and in part because of historical success of vaccines in controlling viral epidemics. There have been two hundred preventive HIV vaccine trials in many countries around the world involving approximately seventy thousand participants (AVAC, 2013a). These trials are discussed in more detail later in the chapter.

### 2.1.2 THE HIV EPIDEMIC AND RESPONSES IN SOUTH AFRICA

South Africa carries a huge burden of HIV infection even though the country has only a fraction of the world's population (Abdool Karim et al., 2009). South Africa remains the country with the largest HIV epidemic in the world (Kavanagh, 2014). UNAIDS (2013)

estimates that in the year 2012 there were 6100 000 South Africans of all ages living with HIV, that the adult prevalence rate was 17.9%, and that 240 000 AIDS deaths and 370 000 new HIV infections occurred in that year. South Africa has a generalised HIV epidemic - fuelled by heterosexual transmission - that constitutes one of its largest public health threats (Abdool Karim et al., 2009; Padayatchi, Naidoo, Dawood, Kharsany & Abdool Karim, 2010). Age-differential partnering, and multiple concurrent and sequential sexual relationships, are among the key drivers of the South African epidemic (Abdool Karim et al., 2009). Conditions created by Apartheid - forced human settlement, land appropriation, migrant labor, the destruction of family life, and income inequality - also facilitated the spread and impact of HIV as well as a range of other health problems (Abdool Karim et al., 2009; Coovadia, Jewkes, Barron, Sanders & McIntyre, 2009).

In South Africa, the response of the Apartheid government to HIV was inadequate and the response of the first democratic government (1994-1999) was muted while nation-building and stability were pursued. The response of the subsequent government to HIV (in the early 2000's) was characterized by denial, dissident views and obstruction (Abdool Karim et al., 2009; Abdool Karim & Abdool Karim, 2010; Achmat & Simcock, 2007; Coovadia et al., 2009). Only in 2007 was a comprehensive national strategic plan launched to combat HIV (SANAC, 2007). The Mbeki government initially resisted the implementation of a free ART program in the public sector, but in response to a concerted advocacy campaign the government released a comprehensive HIV treatment and care plan in 2003 (Abdool Karim, 2011; Johnson, 2012; SA GCIS, 2003; TAC/Section27, 2013). In 2004 when national public-sector ART roll-out commenced (Achmat & Simcock, 2007), the delay had already caused about 330,000 unnecessary deaths (Chigwedere, Seage, Gruskin, Lee & Essex, 2008 in Abdool Karim, 2011).

After the launch of public sector ART roll-out, the total number of South Africans initiated on ART has grown steadily from 47500 to 1,79 million patients during the period 2004 to mid-2011 (Johnson, 2012). National treatment guidelines were promulgated in 2004 and later revised. Revisions have included raising the threshold for ART-initiation from a CD4 count of 200 to 350 for all adult HIV patients as well as a shift from cheaper but more toxic twice-daily dosed ARVs to better tolerated once-daily ARVs in first-line regimens (Johnson, 2014;

Njuguna, Orrell, Kaplan, Bekker, Wood & Lawn, 2013; SA NDOH, 2010; Venter, 2013). The implementation of a national program for the Prevention of Mother to Child Transmission (PMTCT) of HIV began in 2000 and has evolved from a simple preventive regimen during labor and immediately after delivery to include more effective but more complex regimens, and now rates of mother to child transmission are down from 30% to about 3% (Venter, 2013).

Other achievements in South Africa's HIV treatment program have included the expansion of facilities providing ART, a nationwide effort to decentralize ART services into existing primary healthcare facilities (Nglazi, Kaplan, Orrel, Myer, Wood, Bekker & Lawn, 2013), scaled-up HIV testing, the development of simple reliable rapid HIV tests, the development of new categories of health-care workers, and provision of treatment literacy training to HIV patients (Abdool Karim et al., 2009) as well as better integration of HIV programs with TB and antenatal programs (Venter, 2013). Presently, the South African government is implementing the largest HIV treatment program in the world with approximately two million adults initiated on ART in the public sector (TAC, 2014; TAC/Section 27, 2013). While South Africa has underwritten the bulk of its own HIV budget for the past five years, it also receives the most PEPFAR funding – 500 million USD annually (Katz, Bassett & Wright, 2013). Kavanaugh (2014) noted that by the end of 2010, PEPFAR was directly supporting 1 million South Africans on ARVs, and by June 2014, this was down to 30,000 as HIV patients transitioned to government-supported facilities in line with recent shifts in PEPFAR policy.

It has been argued that inaccessibility of ART is largely a thing of the past, however, there are several critical remaining challenges in HIV treatment (TAC/Section 27, 2013). Challenges include deficits in human resources, staff migration and weak management and leadership (Abdool Karim et al., 2009; Coovadia et al., 2009). Challenges include long wait times at clinics, overstretched staff, and poor treatment of patients by health care workers (Abdool Karim, 2011; Kavanaugh, 2014; TAC/Section 27, 2013). Vulnerable procurement of supplies, poor forecasting, late ordering and inadequate distribution has led to stock-outs of ARVs at clinics in various provinces (Abdool Karim et al., 2009; Kavanaugh, 2014; TAC/Section 27; Venter, 2013). Venter (2013) noted that in 2012 stock-outs of one of the first-line adult ARVs meant many HIV patients had the drug substituted with less well tolerated but more available

ARVs. It has been observed that as South African patients supported at specialized PEPFAR-created treatment centres transition to government-run clinics (in keeping with recent shift in policy) HIV patients may face longer wait times, drug shortages or stock-outs, less confidentiality, more stigma, and less attentive care (Katz et al., 2013).

Stigma has been identified as a major barrier to seeking treatment and care (Abdool-Karim, 2011). A considerable challenge is ensuring that persons who test HIV-infected remain continuously in care from the time of testing to the time they are placed in long-term treatment; and ensuring that patients are not lost at various stages from the initial HIV test, to receiving CD<sub>4</sub> results, to being initiated on ART (Hallett & Eaton, 2013; TAC/Section 27, 2013). It is estimated that 40-50% of patients are lost between HIV testing and becoming eligible for ART (Nglazi et al., 2013; TAC/Section 27, 2013). Many infected persons only present for testing and treatment when their CD<sub>4</sub> counts are low and they experience clinical symptoms (Abdool Karim, 2011; TAC/ Section 27, 2013). Operational deficiencies in the PMTCT program include late booking and high loss to follow up after ART initiation (Venter, 2013). Not all South African citizens who need ART are currently receiving it (Johnson, 2012; TAC/ Section 27, 2013). It has also been noted that SA treatment guidelines have generally broadly followed WHO guidelines, but there has often been a delay in promulgating amendments, and there is still restricted access to more expensive ARVs (especially for patients experiencing resistance to HIV) and treatment-initiation at a lower CD<sub>4</sub> count, pointing to differences between what state-dependent patients in South Africa and their 'counterparts in New York or London' might receive (Venter, 2013, p. 40).

In addition to HIV, South Africa faces a range of other health problems, including TB, as well as non-communicable diseases such as diabetes, hypertension, respiratory disease, obesity and substance misuse (Abdool Karim et al., 2009; Mayosi, Flisher, Lallo, Sitas, Tollman & Bradshaw, 2009; Puoane, Tsolekile, Caldbrick, Igumbor, Meghnath & Sanders, 2013). STIs are 'endemic' in South Africa and 'constitute sexual and reproductive health problems in themselves as well as exacerbating HIV infection' (Ramkissoon, Searle, Burns & Beksinska, 2010, p. 38). Government policy for STIs is syndromic management that relies on the diagnosis of symptoms and signs (syndromes), and the provision of antimicrobials to cover most causative agents of presenting symptoms (Lewis & Maruma, 2009; Sonko et al., 2003).

Syndromic management is available at all primary health clinics in South Africa, although problems with service quality – including judgmental attitudes from providers – have been noted (Ramkissoon et al., 2010).

South African women also face unacceptably high rates of unintended pregnancy (SA DoH, 2012a). Hormonal contraception is freely available in public-sector clinic facilities with injectables being the most prevalent (Ramkissoon et al., 2010). Certain study results have raised a possible link between injectable hormonal contraceptives, particularly progestogen-only injectables, and an increased risk of HIV infection (WHO, 2012). The full range of contraceptive options is not always available to women, such as intrauterine devices or IUDs, because of training requirements, and need for sterilization services and cost (Hanes, Vyes & Ruiz, 2009; Ramkissoon et al., 2010; Raymond et al., 2007)

Less than 15% of South Africans belong to private-sector medical schemes, and most South Africans are wholly dependent on the public sector for all their health-care services (Coovadia et al., 2009). Challenges facing the public sector for delivering services for HIV also extend to services for other conditions, and it has been argued that colonial and Apartheid policies and practices resulted in fragmented, under-funded health services generally for the majority of South Africans (Coovadia et al., 2009; Chopra et al., 2009). The post-Apartheid government has achieved a consolidated, comprehensive, better funded public-sector service-delivery system, and expanded programs in primary health-care settings. The public-sector health-care system operates at several levels - community-level services provided at community health centres, primary-level services provided at primarily nurse-run clinic facilities, district-hospital level services including services provided by generalist doctors, regional hospitals with services provided by specialists and tertiary hospitals with services provided by sub-specialists (Chopra et al., 2009). However, it has been argued that inadequate staffing, poor stewardship and inadequate implementation or monitoring of policies remain a challenge to public-sector service-delivery, despite South Africa's status as the wealthiest country in Sub-Saharan Africa (Chopra et al., 2009; Coovadia et al., 2009; Kavanagh, 2014). The morale and attitude of staff, threats to privacy and long wait-times are recognised challenges (Chopra et al., 2009; Sonko et al., 2003).

Regarding the HIV epidemic specifically, South Africa has recognized the combination approach to HIV prevention recommended internationally and has also endorsed efforts to develop novel biomedical interventions in concert with the scale-up of existing strategies in its national strategic plan (SANAC, 2012; UNAIDS, 2011). In South Africa, government HIV prevention initiatives currently encompass information campaigns, detection and early treatment of STIs using a syndromic management approach, condom provision, post-exposure prophylaxis, voluntary male medical circumcision, counselling and testing, and PMTCT (Lewis & Marumo, 2009; Padayatchi et al., 2010; SANAC, 2012). The South African government has also stated its commitment to support research into experimental HIV vaccines in both national strategic plans (SANAC, 2007; 2012). South Africa's latest plan states that the 'search for a highly efficacious and safe vaccine remains a beacon' in the quest for prevention innovations (SANAC, 2012, p.67). HIV vaccine trials in South Africa are reviewed later in this chapter.

### 2.1.3 HEALTH RESEARCH WITH HUMAN PARTICIPANTS

The objective of health research - to develop generalizable knowledge pertaining to human health – is a recognized good, however research has the potential to treat participants merely as means to an end therefore stringent efforts must be made to ensure participants are treated with dignity and respect while they contribute to the social good (Emanuel et al., 2000). The core issue is determining what is owed to fellow human beings who take part in research initiatives largely designed to benefit others (Presidents Commission, 2011). Human participants in health research assume risks and burdens linked to research procedures and participation, while the benefits in the form of increased knowledge or health interventions may largely accrue to future persons (cf. Emanuel et al., 2000; NBAC, 2001). To address the central issue of how best to involve humans in potentially risky endeavours for the benefit of others or how best to reconcile the 'rights of individual persons with the demands of the scientific enterprise' (Emanuel et al., 2003, p. 1), a number of broad ethical principles have been articulated (National Commission, 1979). In addition, there has been the development of dedicated ethical guidelines outlining standards for the conduct of health research with human participants (WMA, 2008; 2013) including in low-resource settings (CIOMS, 2002) as well as the articulation of systematic ethical frameworks for the review of health research

with human participants (Emanuel et al., 2000; Emanuel, Wendler, Killen & Grady, 2004; Emanuel, Wendler & Grady, 2008). Such guidance also applies to clinical trials designed to answer questions about the safety and efficacy of interventions in human participants such as drugs, devices and vaccines.

The broad principles commonly held to apply to health research (including HIV vaccine trials) include respect for persons, beneficence and justice. A common formulation of *respect for persons* is that researchers, firstly, should respect peoples' decisions and actions, and secondly, should protect persons with impaired or diminished autonomy (CIOMS, 2002; National Commission, 1979). A common formulation of *beneficence* is that researchers should maximise potential research-related benefits and minimize potential research-related risks and ensure the potential risks to participants are reasonable in light of expected benefits, as well as refrain from deliberately inflicting harm (CIOMS, 2002; National Commission, 1979). It has been observed that there are many formulations of justice applied to research (Macklin, 1998), however a common formulation is that of distributive justice – that there should be a fair distribution of research-related burdens and benefits among the collaborating parties, and no single group should bear a disproportionate share of the risks nor access a disproportionate share of the benefits (Grady, 1996). It is widely recognized that ethical principles are formulated at a fairly abstract level, and they must be specified and applied to actual cases, and it is at this level that ethical commentators may reach different conclusions about the right course of action (CIOMS, 2002; Emanuel et al., 2008). They are held to be 'universally germane although variations in interpretation and application are expected' (Grady, 1996, p. 44). Furthermore most situations involve or implicate more than one principle, which often requires that the involved principles be balanced against each other (Emanuel et al., 2008).

There have been efforts throughout the world to strengthen ethical responses to health research involving human participants, for example by strengthening the legal framework for health research, by developing comprehensive ethical guidelines for health research, by building the skills of researchers and RECs to understand and implement key ethical protections for participants and by raising awareness of participants themselves about their rights (cf. Emanuel et al., 2003; Emanuel et al., 2008; Macklin, 2009; NCOB, 2002). There has

been an increasing investment in research ethics capacity-development throughout the world in order to keep pace with the increasing amount and complexity of health research being conducted often in low-resource, culturally complex settings (Ijsselmuiden, Marais, Wassenaar & Mokgatla-Moipolai, 2012; Ndebele et al., 2014). These investments have focused on training RECs and strengthening REC infrastructure, and funders have included the National Institutes of Health, the Wellcome Trust and the European Developing Countries Clinical Trials Partnership (Ndebele et al., 2014).

#### 2.1.4 HEALTH RESEARCH WITH HUMAN PARTICIPANTS IN SOUTH AFRICA

South Africa has also strengthened its ethical response to health research with human participants generally by establishing the National Health Research Ethics Council to (amongst others) register and audit health RECs, by developing draft human subjects regulations (SA Government, 2013) and by releasing national ethical guidelines governing health research (SA DOH, 2004), and clinical trials (SA DOH, 2006). The country has over thirty RECs registered with the National Health Research Ethics Council (SA DOH, 2012b). Some of these were established as early as 1977 and have a long history of protocol review (Cleaton-Jones & Wassenaar, 2010). There have been efforts to set up research ethics capacity training initiatives for South and Southern African RECs (Ndebele et al., 2014). Such responses are especially critical in the light of research abuses that have taken place in South Africa including of military soldiers (Baldwin-Ragaven, de Gruchy & London, 1999) as well as participant vulnerabilities such as low educational attainment or low research literacy. Since the implementation of s73 of the South African National Health Act (SA Government, 2003) it is a legal requirement for all health research within South Africa to be reviewed and approved prior to its commencement by a REC registered with the National Health Research Ethics Council.

## 2.2 HIV VACCINE TRIALS

### 2.2.1 AIMS, PHASES AND STAKEHOLDERS IN HIV VACCINE TRIALS

Trials of HIV vaccines explore whether experimental vaccines given to *HIV-uninfected* persons can prevent HIV-acquisition or lessen AIDS disease (so-called preventive HIV vaccine trials) and they also explore whether experimental HIV vaccines given to *HIV-infected* persons can boost the immune system in order to better control the infection (US DHHS, 2006) (so-called therapeutic HIV vaccine trials). The focus here is on preventive HIV vaccine trials. Preventive HIV vaccine trials take place in specific phases. *Phase I trials* aim to explore the safety and tolerability of experimental vaccines and enrol small numbers of participants at low risk of acquiring HIV infection. They typically take twelve to eighteen months to complete. *Phase II* trials aim to explore the safety and ability of vaccines to induce promising immune responses in a larger number of participants, as well as dosage, regimens and routes of administration. They typically take about two years to complete. *Phase III trials* (efficacy trials) aim to explore whether experimental vaccines can prevent HIV infection (a so-called primary endpoint) or ameliorate disease progression (a so-called secondary endpoint) and these trials enroll thousands of participants at risk of acquiring HIV (Abdool Karim, 2002). They take about three to five years to complete. Phase III trials form the basis for regulatory rulings about whether experimental vaccines will be approved and licensed (WHO/UNAIDS/IAVI, 2006). Another phase has recently been introduced – namely phase IIB trials that aim to provide proof of concept or information about whether candidate vaccines should be moved into phase III trials or rather reformulated or even abandoned altogether (WHO/UNAIDS/IAVI, 2006). In all phases, participants are randomised to receive either experimental vaccine or placebo, and they are 'blinded' to which groups they are in (as are researchers).

HIV vaccine trials bring together a range of stakeholders involved in their implementation – agencies that develop experimental HIV vaccines which are often but not exclusively large multi-national pharmaceutical companies, and trial sponsors who finance such trials, and networks who co-ordinate the conduct of trials (often in co-operative agreements with trial sponsors). Public-sector funding – largely from US-based public agencies - constitutes the bulk of sponsorship for HIV vaccine trials, and it has been calculated that the US National

Institutes of Health sponsored 20 of the 33 HIV vaccine trials that were being implemented in 2011 (HIV vaccines and microbicides resources tracking group, 2012). This sponsor has published official guidance on ART-access only in relation to participants in HIV treatment trials which recommends that researchers collaborate with local authorities to identify post-trial sources of ART (Shah, Elmer & Grady, 2009).

HIV vaccine trials also involve site-staff who recruit, enrol and retain participants over the course of trials including principal investigators responsible for the overall conduct of such trials at specific sites. They involve Research Ethics Committees (RECs) who review trial protocols for ethical rigor, and regulatory authorities who review such trials for scientific quality and product safety (cf. Tarantola et al., 2007). They also involve members of participating communities who are often represented in a formal structure termed a Community Advisory Board or CAB.

HIV vaccine trials also involve participants who come for many trial visits over extended time frames and who take part in multiple trial procedures – some of them invasive. Participants undergo physical examinations and provide detailed medical histories to establish their overall health and provide a baseline against which adverse events can be measured. They undergo repeated HIV testing at regular time-points to establish if they have acquired HIV infection over the course of the trial. They undergo regular assessments of their sexual risk to monitor if this changes over the course of trials. They undergo assessments for STI infection. Female participants are counselled to avoid pregnancy, are required to take reliable contraception to avoid pregnancy, and are tested regularly for pregnancy during the vaccination period to prevent pregnant women from exposure to experimental HIV vaccines because safety to pregnant women and unborn children is usually not known (Latka et al., 2012; Macklin, 2010b). Participants undergo blood draws for laboratory testing to assess the reactions of their immune system. Participants also receive regular administrations of either experimental vaccine or placebo, and report on their reactions (cf. Gray et al., 2011; UNAIDS/WHO, 2012). They take part in detailed assessment of social harms or social adverse events that may have occurred because of their participation (such as experiences of stigma or discrimination). To meet ethical responsibilities to prevent HIV, researchers and sponsors also ensure that participants take part in counselling sessions to help them decrease their HIV

risk as well as receive access to prevention methods such as STI treatment, male and female condoms, male circumcision and post-exposure prophylaxis (Essack, 2014; Macklin, 2009). These trials also involve volunteers - persons who present for enrolment into HIV vaccine trials and take part in screening procedures but do not become participants because they do not meet the eligibility criteria, for example, they may already be HIV infected or they may have a pre-existing medical condition that disqualifies them from participating.

It has long been recognized that trials of experimental HIV vaccines are ethically complex due to several features including partnering between countries and institutions with varying economic resources, power and cultural inheritances, as well as the complex nature of the trial designs, and participating community mistrust based on past exploitative interactions (cf. Guenter et al., 2000; MacQueen, Harlan, West Slevin, Hannah, Bass & Moffet, 2012; WHO/UNAIDS, 2004; WHO/UNAIDS, 2006). A critical feature that raises the ethical complexity of such trials is that persons vulnerable to HIV infection need to be enrolled in late-phase trials (indeed such persons are the intended beneficiaries of vaccines) but such persons often have other vulnerabilities such as impoverishment, marginalization, poor education, low literacy, and little experience with research that may compromise their consent abilities or increase their susceptibility to research risks (UNAIDS, 2000a). Recognition of this central tension led to the early development of specialized ethical guidelines (UNAIDS, 2000b) subsequently revised (UNAIDS/WHO, 2007; 2012). It was recognized that experimental HIV vaccines are targeted against a debilitating, highly stigmatizing condition requiring life-long care and treatment (UNAIDS, 2000a, UNAIDS 2000b).

It was also noted that participation would entail potential risks, or the possibility of various harms, some of them serious or severe. For example, vaccinees might experience enhanced susceptibility to HIV infection if exposed to the virus (the opposite effect to that hoped for). Also vaccinees might produce antibodies causing them to have a positive antibody test result on some types of HIV tests even when they are not HIV-infected – so-called Vaccine Induced Sero Positivity or VISP – which may last for an indefinite period. It was also recognized that participation might impose a number of burdens on participants, such as having to attend numerous visits, or lead to certain restrictions, such as having to refrain from donating blood

while enrolled, or having to test for HIV only at facilities capable of distinguishing VISP from true infection (cf. Allen, 2001). The latter burdens and restrictions are perhaps best understood as 'hardships' associated with participation (cf. Ulrich, Wallen, Feister & Grady, 2005, p. 17).

Recognition of the ethical complexity of HIV vaccine trials has long been coupled with recommendations to promote the rights and welfare of participants by strengthening ethico-legal frameworks and developing the ethical expertise of key vaccine stakeholders (Global Enterprise, 2012). African countries (and other low to middle income countries) in particular were encouraged to develop their ethico-legal frameworks, and stakeholder capacity to address the complex ethical issues in such trials (Kaleebu et al., 2008) including REC capacity (Klitzman, 2007). There has been a concerted effort to mobilize key stakeholders to participate fully in the HIV vaccine development process with the establishment of advocacy organisations such as the AIDS Vaccine Advocacy Coalition (AVAC) as well as efforts by trial sponsors and networks to develop the capacity of key constituencies to impact on trials through the development of resources and mechanisms for their participation (GCM, 2004; IAVI, 2009; Kahn, 2005; NIH, 2011; Snow, 1999). There have also been efforts to analyse common problems and share resources across vaccine trials targeted against HIV, malaria and TB (Grady, 2004; Mamotte, Wassenaar, Koen & Essack, 2010).

Key ethical complexities in HIV vaccine trials include, but are not limited to: ensuring optimal engagement of community and other stakeholders in the design and conduct of trials (MacQueen et al., 2012; UNAIDS/AVAC, 2011); offering participants prevention modalities to prevent them acquiring HIV (Dawson, 2012; Macklin, 2009); and offsetting social harms to participants such as stigma and discrimination (Allen, 2001; Fuchs, Durham, McLellan-Lemal, Vittinghoff, Colfax, Gurwith & Buchbinder, 2007). They also include ensuring sound informed consent for participation (Coletti, Heagerty, Sheon, Gross, Koblin, Metzger & Seage, 2003; Woodsong & Abdool Karim, 2005), ensuring appropriate enrolment of sub-populations at risk of HIV infection such as adolescents (WHO/UNAIDS/AAVP, 2007) and ensuring vaccinees have long-term access to HIV tests that can distinguish between an antibody response (VISP) and true HIV infection, as well as access to appropriate explanatory documentation and support from trial sites to prevent and address the negative consequences that may result

from a false diagnosis of HIV infection (Cooper, Metch, Dragavon, Coombs & Baden, 2010; Fuchs et al., 2007).

### 2.2.2 HIV VACCINE TRIALS IN SOUTH AFRICA

In South Africa, HIV vaccine research has been coordinated through SAAVI. SAAVI was established in 1999 as a lead project within the Medical Research Council with funding from government and non-governmental sources (Galloway, 2000). From its inception, SAAVI funded empirical and conceptual research and resource development to address ethical complexities as an integral component of such trials (cf. Galloway, 2000). Social-behavioural research itself has long been acknowledged as integral to such trials (Koblin, Andrasik & Autin, 2013; Newman, 2012).

In South Africa, eight HIV vaccine trials have been completed since 2003, and four more trials are ongoing (Emily Donaldson, personal communication, 13 August, 2014). These have comprised a mix of phase I and II trials, and one large-scale phase IIB trial. There are five sites currently implementing HIV vaccine trial protocols, however, a large site expansion is currently underway in preparation for a phase III licensure trial slated to begin in 2015 (AVAC, 2013b) that will explore more definitively whether an experimental HIV vaccine can prevent HIV infection or ameliorate disease progression in thousands of participants at risk of acquiring HIV. These trials of experimental HIV vaccines form one part of broader efforts to conduct trials of non-vaccine prevention modalities in South Africa including voluntary male circumcision and microbicides (Ramjee et al., 2010). AVAC (2013c) calculated that in 2013 there were fourteen ongoing biomedical HIV prevention trials taking place at fifteen different locations in South Africa.

There have been efforts to address ethico-legal complexities for HIV vaccine trials specifically in the South African setting including but not limited to how to better ensure the engagement of key stakeholders such as the participating community (Lesch, Kafaar, Kagee & Swartz, 2006; SAAVI, 2007; Swartz & Kagee, 2006) or civil society (Koen, Essack, Slack, Lindegger & Newman, 2013); how to ensure a sound standard of prevention (Essack, Slack,

Koen & Gray, 2010); how to promote authentic consent given participant vulnerabilities and cultural complexities (Lindegger & Richter, 2000) including sound ways of assessing if participants have comprehended complex trial information (Lindegger, Milford, Slack, Quayle, Xaba & Vardas, 2006), and how to prepare for adolescent enrolment (Slack, Strode, Fleischer, Gray & Ranchod, 2007; Strode & Slack, 2013; Strode, Toohey, Slack & Bhamjee, 2013). South Africa has also developed dedicated guidance for HIV vaccine trials (SA MRC, 2003) by adapting international ethical guidelines on the topic (UNAIDS, 2000b). Efforts are also underway to develop a national strategic plan for HIV vaccine development that includes broad ethical protections for participants (SA DOH, 2012c).

## **2.3 THE DEBATE ABOUT CARE IN HIV VACCINE TRIALS**

### **2.3.1 INTRODUCTION**

As mentioned in earlier sections, HIV vaccine trials enrol persons who tend to be generally healthy and are also not infected with HIV. Over the course of trials, some participants will acquire HIV infection because of on-going risk behaviour despite access to methods designed to decrease their risk of HIV acquisition, such as counselling, condom promotion, STI treatment and male circumcision (Dawson, 2012; Essack, 2014; Haire, Kaldor & Jordens, 2012; Macklin, 2009). In late-phase trials enrolling participants at higher risk of HIV infection (phase IIB or III) it is even more likely that some participants will acquire HIV infection than in early trials enrolling participants at low-risk of HIV infection. Late-phase trials seek to establish (in the first instance) whether experimental HIV vaccines can prevent HIV infection in vaccinees compared to placebo-recipients or (in the second instance) to establish whether experimental HIV vaccines can ameliorate disease progression in vaccinees who acquire HIV infection, compared to placebo-recipients (Abdool-Karim, 2002). Therefore in late-phase trials HIV infection is a trial endpoint that is explicitly measured, as are markers of disease progression such as viral load measures, CD4 counts and the time it takes to reach ART (Kim, Tabet, Corey & Celum, 2005). It is therefore important to the scientific success of such trials to identify and track HIV in trial participants, however, it is not part of the scientific objectives to provide treatment and assess treatment responses as it would be in an HIV treatment trial (cf. Richardson, 2007).

Early in the design of HIV vaccine and other prevention trials, access to ART was scarce in many resource-poor settings (MacQueen, Shapiro, Abdool Karim & Sugarman, 2004). In many countries, ART was not available through national public-sector care, and efforts to scale up access through donor-funded initiatives were either absent or in their infancy. From early 2000 and continuing throughout the decade, there was intense debate about the obligations of sponsors and researchers towards participants acquiring HIV during such trials who resided in low-resource settings with little access to effective treatment (Bass, 2004; Bloom, 1998; Guenter et al., 2000; Heise, McGrory & Wood, 1998; SA MRC, 1998; WHO/UNAIDS, 2004; UNAIDSa; UNAIDS, 2000b). It was recognized early that large sponsors of HIV vaccine trials such as the National Institutes of Health based in the United States may have regulatory restrictions on using research funds to provide care unless such care is necessary for the scientific protocol (cf. Philpott, West Slevin, Shapiro & Heise, 2010). However the relative power and access to resources of trial sponsors - and other industrialized-country collaborators - sparked intense debate about how HIV infections in trials should be addressed when it was predictable that participants in low-resource settings would face inadequate treatment.

The specific debate in HIV vaccine trials focussed on HIV infection, and the problem of inadequate access to ART, but it occurred alongside a broader debate about researchers' responsibilities to implement responses addressing participants' medical needs in low-resource settings when such responses would not service the scientific objectives, nor keep participants safe (Belsky & Richardson, 2004) – their so-called 'ancillary care' responsibilities – *particularly when responses might be costly or demanding*. Within HIV vaccine trials, there were also calls to avoid allowing a focus on ART-access to eclipse the broader spectrum of care needs that participants may present with (GCM, 2005). The debate in HIV vaccine and other prevention trials has expanded to include researchers' responsibilities towards other needs identified in trials (Heise et al., 2008; MacQueen & May, 2008; Ngongo et al., 2012); as well as towards non-participants (Brownsword, 2007) and even the broader community (Weijer & LeBlanc, 2006).

In the debate about HIV vaccine trials, commentators tried to explore the rationale that best grounds sponsor-investigator responsibilities to participants' medical problems, particularly HIV infection. What ethical argument best anchors their responsibilities? Ethical commentators turned to arguments based on 'standard of care' (Guenther et al., 2000; UNAIDS, 2000a), as well as to arguments based on broad ethical principles in research ethics (cf. Macklin, 2006a; Shapiro & Benatar, 2005; Slack, Stobie, Milford, Lindegger, Wassenaar, Strode & IJsselmuiden, 2005) and lastly to arguments based on emerging ethical frameworks (Dickert & Wendler, 2009; Richardson, 2007). In the section that follows, these arguments are examined in more detail.

### 2.3.2 STANDARDS OF CARE

Some commentators (UNAIDSa) argued that sponsors and investigators should ensure that HIV vaccine trial participants have ART-access, even in settings where it was not available, because participants in clinical trials should receive the 'standard of care'. This term (originally from the medico-legal context) migrated into the research ethics arena and referred to the care to be offered to control-group participants when new interventions were being tested (Heise et al., 2008; NBAC, 2001). The term standard of care framed intense debate about the conditions under which it was ethically acceptable to test new interventions against placebo when an effective intervention already existed or, put another way, when it was ethically acceptable to provide some participants with no treatment when effective treatment already existed.

Central to the concept of standard of care is that for any particular medical condition there is a set of recognized treatment and care interventions that constitute the standard of care for that particular condition (Holm & Harris, 2008). The standard of care acts as the baseline against which other treatment regimens can be compared in a clinical trial (Holm & Harris, 2008). However it has been recognised that the concept of standard of care is more ambiguous than it first appears, and that a number of standards exist under the rubric of standard of care (Macklin, 2008) or put another way the term can be indexed to various points of reference (Heise et al., 2008). More specifically, there is the *de facto standard* which is the actual set of practices for medical patients in a community (often determined

empirically) and the normative or *de jure* standard of what should be provided to patients as determined by medical experts. The latter can be (in itself) the local *de jure* standard as defined by national treatment norms and guidelines, national regulatory authorities and national experts in a particular country or it can be the global *de jure* standard as defined by global experts and authorities such as WHO and encompassing the best proven interventions available anywhere in the world (London, 2001; McGrory, Philpott, Hankins, Paxton & Heise, 2010). The latter standard of the best treatment available anywhere in the world is sometimes referred to as the universal standard (NCOB, 2002).

The case that opened up the debate about the standard of care for control-arm participants (Holm & Harris, 2008) was the perinatal HIV transmission trials in developing countries that compared a short-course antiretroviral regimen (zidovudine) to placebo instead of to a more expensive and logistically more complex longer-course regimen previously shown to be effective (Bayer, 2000; NCOB, 2002). Critics of placebo-control argued that no participant taking part in a trial supported by United States (US) funds should be denied the standard of care available there, and that known effective treatment should not be withheld from participants. In support of this argument the Declaration of Helsinki (WMA, 1996, II.3) was cited - *'In any medical study, every patient, including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of placebo where no proven ...method exists.'*

Defenders of placebo control noted that the standard of care available in high-income countries was at that time unaffordable in low-resource-settings and logistically difficult to implement as a part of routine antenatal care (Holm & Harris, 2008) – on the latter point it required mothers to cease breastfeeding, use formula and risk infant diarrhoea (cf. van der Graaf & van Delden, 2009). They argued that in resource -poor settings, it was acceptable to test a simpler cheaper regimen against placebo, where the standard of care available in high-income countries was not available or sustainable in the low-resource setting, and the objective was to develop safe and effective interventions that were responsive to critical health needs and priorities in that setting (Bayer, 2000). Defenders of placebo-control argued that comparing a shorter cheaper regimen to a longer, more expensive regimen would not represent a research question of high value in many low-resource settings, and that it was

critical to ensure that trials addressed concerns that were locally relevant and were designed to benefit the actual population from which participants were drawn (Holm & Harris, 2008). Effectively defenders of placebo-control argued that incorporating the global *de jure* standard in this case would render the research question locally irrelevant (DAIDS, 2010) or would provide information that was not useful to patients in that setting (Holm & Harris, 2008) or would ensure that the results were of more value to the researcher than the researched community (van der Graaf & van Delden, 2009). This debate illuminated that while commentators agreed that control-arm participants should get 'standard of care' they did not agree about the best moral guide for determining the standard (McGrory et al., 2010). Resnik (2014) argued that debate illuminated underlying disagreement about what it means to not exploit participants.

This ethical controversy about the standard of care to be offered to control-arm participants in perinatal transmission studies involved collaborative research between investigators and participating communities from low-resource settings on the one hand, and sponsors from high-income countries on the other. It also involved allegations that the existence of effective ART made a central feature of the trial unethical (that is, use of placebos), as well as counter-charges of ethical imperialism and insensitivity to realities in low-resource settings. It was argued early on that the placebo-control debate underscored the need to seriously consider the implications for HIV vaccine trials in developing countries with inadequate ART-access (Bloom, 1998).

The controversy in these perinatal transmission studies centered on the question 'when is it acceptable to compare a new treatment against placebo when a proven therapeutic method exists' and the terminology 'standard of care' referred to the standard against which new interventions are to be tested. In HIV vaccine trials, commentators extrapolated the term standard of care to the issue of HIV treatment in under-resourced contexts, asking the question: 'when is it acceptable to provide less than best proven treatments to participants who acquire HIV while enrolled in trials'? The debate in HIV vaccine trials came to focus on three levels of HIV treatment, more specifically the debate focused on whether participants should receive HIV treatment and care (i) at the 'best proven' treatment standard or (ii) at the

local standard or (iii) at the 'highest attainable' standard? (Guenter et al., 2000; Macklin, 2008; UNAIDS, 2000a; UNAIDS, 2000b).

Some commentators argued participants should receive the 'best proven' treatment available internationally including ART according to best scientific evidence available at the time of the trial (Guenter et al., 2000; Levine, 1999; UNAIDS, 2000a) or put another way according to 'what is available to participants in the same or similar trials in industrialized countries' (Macklin, 2008, p. 284) and participants should not be consigned to receive the often inadequate prevailing care in low-resource settings (Lurie & Wolfe, 1999; Macklin, 2008). Some commentators countered that the 'best proven' standard was problematic insofar as it confined the focus to the equivalency of drug regimens between participants from high-income and low-income settings (Benatar & Singer, 2000; Benatar, 2002). It was argued that this was somewhat arbitrary and de-emphasized other care components, such as access to equivalent facilities or personnel with equivalent qualifications or expertise (Benatar & Singer, 2000; Benatar & Singer, 2010).

Critics also argued that applying the 'best proven' standard in HIV vaccine trials would mean that sponsor-investigators would be saddled with financing and providing ART for extended periods, which would exhaust limited funds or overwhelm study budgets (Grant et al., 2006). It was also argued that it would require clinical skills not available in research teams and require scarce monitoring infrastructure (Guenter et al., 2000). Critics asserted that study sponsors would be deterred and the progress of trials would be adversely affected (cf. Macklin, 2006a). Still others argued that the 'best proven' standard could be exposed as untenable by invoking it in other trials, for example, application of that standard in trials exploring whether aspirin would reduce death from heart attacks or strokes would require needy participants to be provided with angioplasty or coronary artery bypass surgery (Bloom, 1998).

At the other end of the spectrum, some argued that participants in HIV vaccine trials should receive the 'local standard' – that which would be routinely available to them in the public sector in their country. It was asserted that participants would not be made worse off by their participation as they would not be deprived of treatment that would otherwise have been

available in their setting, and to which they consented (Resnik, 2014; UNAIDS, 2000a). Critics argued that this position would consign participants to the inadequate treatment delivered to patients in the public-sector health systems of low-income countries, take advantage of the negative conditions prevailing in many resource-poor settings, violate the Declaration of Helsinki (Lurie & Wolfe, 1999; UNAIDSa) and fail to provide participants with important benefits (Resnik, 2014).

Other commentators promoted yet another standard for participants in HIV vaccine trials who acquired HIV- the so-called 'highest attainable' standard (UNAIDS, 2000b). The 'highest attainable standard' was viewed as the standard of medical services available for patients in the local setting combined with the additional resources brought by the sponsor into the research setting (Guenter et al., 2000; UNAIDSa; UNAIDS, 2000b). Harris (1998) asserted that it could not follow from the fact that researchers cannot do everything that they are permitted to do nothing. He argued that researchers could not move from the impossibility of providing everything to the conclusion that participants should get inadequate prevailing local care. He noted the question must be what should reasonably be provided by researchers taking into account all the circumstances of the study? (Harris, 1998). While 'highest attainable' might be viewed as somewhat vague, it clearly expressed the spirit that sponsors and researcher should take steps to improve care services for participants, by for example, building infrastructure and capacity to deliver strengthened services (Guenter et al., 2000). This approach to the issue of treatment-access tended to foreground participants' access to ART for HIV needs specifically.

### 2.3.3 ETHICAL PRINCIPLES

Some commentators argued that a sound justification underpinning responsibilities for participants needs was that of *reciprocal justice*. Reciprocal justice calls for providing something in return for the contributions participants have made (NBAC, 2001 in Macklin, 2006a; 2006b). It was argued that participants 'who place themselves at some risk, enduring discomfort and inconvenience, deserve something in return for their efforts in contributing to a search for an efficacious vaccine' and therefore ART-access should be assured for participants (Macklin, 2008, p. 284). Furthermore, it was asserted that late-stage trials cannot

draw conclusions about efficacy without participants' HIV infections (Macklin, 2006a). Some have agreed that the notion of 'returning good for good' seems sensible (Merritt & Grady, 2006, p. 1792) and that reciprocity may be relevant where participants have assumed risks to generate research findings (Shah et al., 2009).

However some commentators have raised questions about reciprocity-based accounts of researcher obligations (Merritt & Grady, 2006; Shah et al., 2009). Some critics countered that one is grateful not only to those participants who become HIV-infected but also to those who do not, and that those that remain un-infected also deserve a commensurate response (Weijer & LeBlanc, 2006). Therefore, if sponsor-investigators were to provide ART to HIV-infected participants, it seems unfair not to give something commensurate to uninfected participants (Weijer & LeBlanc, 2006, in Stobie & Slack, 2010). It was also argued that while investigators could express gratitude to those participants who become HIV-infected by providing ART, it is also possible that some other expression of gratitude might suffice although when participants assume risks in the domain of health it seems logical the reciprocal responses should follow in the same domain (Stobie & Slack, 2010). Some questioned the extent of the reciprocation required of researchers in response to participants' contributions, for example, is a life-time of HIV treatment an appropriate response? (Millum, 2010). Lastly, some noted that researchers rely on the goodwill, buy-in and risk-assumption of participating communities, and on reciprocal justice accounts, representatives from participating communities may also be viewed as deserving of some response for what they offer raising the question of what health responses should be implemented for participating communities (Stobie & Slack, 2010).

Some commentators explored other justice-based arguments to ground sponsor-investigator responsibilities towards care in HIV vaccine trials. It was recognized that HIV vaccine trials are international collaborations that juxtapose participants from high-income and resource-poor settings either actually (where there is a trial arm in both settings) or hypothetically (where there is no arm in the sponsor country but the sponsor comes from a resourced setting) (cf. Macklin, 2008). This highlighted 'the disparity between what research participants would receive if the trial were undertaken in industrialised countries and what is normally available

in developing countries. A multi-centre preventive vaccine trial ...done simultaneously in industrialised and developing countries poses this stark contrast' (Macklin, 2008, p. 284).

In response to this stark contrast some invoked the principle of *justice as equality* – arguing that infected participants from resource-rich and resource-poor settings should be treated equally, and because participants in high-income settings would receive access to ART, so should participants drawn from low-income settings. It was argued that participants are alike in relevant respects and therefore they should be treated the same regardless of geography (WHO/UNAIDS, 2004). However it was noted that another competing conception of justice was *justice as equity*, which would not require treating participants from different settings in exactly the same way, but would rather require that participants be treated equitably – the latter formulation would allow that participants' access to care be determined based on consideration of what was affordable, feasible and sustainable in the actual setting (WHO/UNAIDS, 2004).

In response to the stark contrast between developing-country trial participants and their developed country counterparts, some noted that researchers should attempt to distribute resources in a way that benefits the worst-off in society, in this case those trial participants who lack access to adequate health-care (Daniels, 1975, in Slack et al., 2005; Stobie & Slack, 2010). However, it was noted that the so-called 'worst off' could be those already long-infected with HIV (namely HIV-infected residents in the participating community), and on this account it is not clear why researchers should provide ART to participants and not to members of the participating community as a better expression of justice (Slack et al., 2005). Furthermore, on such accounts there would be some uncertainty about whether ART for a few participants constituted the best use of limited resources, and whether such resources would not be better spent on more basic health-care for participants, such as adequate nutrition, or TB treatment (Stobie & Slack, 2010).

Other commentators have argued that the principle of *social justice* can be usefully applied to the complex question of care for participants in developing-country prevention research (Guenter et al., 2000; Shapiro & Benatar, 2005). They have asserted that differences in healthcare between sponsor and host countries are inherently unfair in part because

inadequate host-country care is caused by sponsor-country activities, such as current unsound trade rules or past colonialism (Hooper, 2010; Shapiro & Benatar, 2005). They have argued that the proper role of sponsors and investigators in this context includes to help 'reduce gross injustices' (Shapiro & Benatar, p. 41) and to 'bridge the unacceptable gap' between care standards in sponsor versus host countries (ibid, p. 44). On this account, the goal is to incrementally ensure care standards for the host community that are higher than those currently available and are closer to sponsor-country standards. Sponsors and investigators should 'progressively ratchet the standard of care upwards' for participants *and* their communities (ibid, p. 39). Recommended steps included that researchers set aside funds to provide ART for participants acquiring HIV, to address participants' other needs, and to contribute to HIV and reproductive health care for general citizens. On this account, the focus of researchers attention is not necessarily on participants alone, and not necessarily HIV infection alone.

Some have also attempted to delineate an account of ancillary care consistent with the reduction of global health disparities (referring to the earlier work of Benatar & Singer, 2000) by describing what is owed by external research actors from high-income countries encountering health needs of persons in less resourced countries (Pratt, Zion, Lwin, Cheah, Nosten & Loff, 2013). They allocate primary responsibility for health care to the state but assert that where states cannot meet their responsibilities then global actors have an obligation to assist (albeit in a restricted way) to address health conditions. On their account, researchers should deliver health-care for 'a limited subset of conditions that cause severe morbidity and mortality' in the host community (Pratt et al., 2013, p. 1). Researchers and sponsors should implement responses based on functions they typically assume (because these existing functions ensure skills and resources that make them particularly capable) and such responses include for example capacity-building and some financing of care. They assert that claimants of care include actual participants but allow that participants' families are also potential claimants on this account. They assert that the creation of inequalities between participants and non-participants is not desirable and that care responses should not be so extensive that they usurp the research because research is critical to helping achieve justice in global health.

Critics have questioned social justice accounts, by questioning why such obligations would fall on researchers only (Richardson, 2007) or by asserting that many HIV prevention researchers are already demonstrating their commitment to redressing health inequities (Weijer & LeBlanc, 2006). Proponents of such accounts do themselves acknowledge that such accounts would attach responsibilities to non-researchers, and would in fact apply to non-participants, therefore conceding that such accounts of researchers' duties to participants are not 'airtight' (Hooper, 2010, p. 709).

Some commentators have argued that researchers are obligated to provide ART to participants who acquire infection during trial participation because HIV infection can be viewed as a *research-related injury* for which trial participation is responsible (Schüklenk, 2000; Schüklenk & Ashcroft, 2000; Schüklenk & Ashcroft, 2008) and that treatment-access is owed to participants as a kind of compensatory justice (cf. Macklin, 1998). More specifically, these commentators asserted that participants would have false beliefs that the experimental HIV vaccine would protect them from HIV and these misconceptions would lead to increased high-risk behaviour that would lead to HIV acquisition, harming participants, and such harm would be the fault of the trial (Schüklenk, 2000; Schüklenk, & Ashcroft, 2008).

It was counter-argued, however, that these 'compensation for harm' arguments were limited (Macklin, 2006a) because of insufficient evidence to indicate that participants suffer a general 'behavioural disinhibition' while enrolled in trials that could form the basis for a general obligation to treat all HIV infections acquired on trials (Slack et al., 2005). Furthermore, even if certain participants have false beliefs about vaccine efficacy and increased risk behaviour, such participants are conceivably identifiable through assessing their comprehension and risk-behaviour, therefore this is not a sound justification to argue that sponsor-investigators must provide ART for all HIV infections acquired on trials (Slack et al., 2005; Slack & Stobie, 2008). Even in those instances where experimental HIV vaccines themselves were associated with a biologically-mediated increased risk of HIV acquisition, such arguments would logically only apply to specific vaccine products and to specific groups of participants, namely intervention-arm participants and not placebo-arm participants (Stobie & Slack, 2010). Other commentators also concluded that research-related injury was not necessarily a robust argument for grounding the responsibility to ensure ART-access for participants acquiring

HIV infections in trials (Weijer & LeBlanc, 2006). These 'compensation for harm' arguments tended to focus on issues of care for participants specifically and on care for HIV infection specifically.

Some commentators argued that the principle of *beneficence* constitutes a promising principle to ground sponsor-investigators care responsibilities (Shapiro & Benatar, 2005). Macklin (2008) asserted that this principle has been expressed as the obligation of researchers to maximise research-related benefits to participants, as well as to seek to minimize research-related risks, and that 'providing medical treatment to participants who become sick is one way, among others, of maximising health-related benefits' (p. 284). Still others have attempted a fuller elaboration of beneficence-based responsibilities in trials. They asserted that beneficence entails contributing to the welfare of other people, and can be expressed as the maxim that if one can do something beneficial without sacrificing anything of comparable moral significance then it should be done (Singer, 1999 in Stobie & Slack, 2010). Therefore, for example, when HIV treatment can be ensured without undermining the trial itself, then sponsor-investigators should ensure it. However, the authors conceded that on this account beneficence would not be limited to participants, but would extend to non-participants, such as those screened out of trials, nor would beneficent interventions necessarily be limited to HIV treatment or even ART but might well extend to a range of other 'goods' that a capable actor could provide (Stobie & Slack, 2010).

The same authors then turned towards the principle of *specific beneficence* to help clarify care responsibilities, more specifically, the notion that people have specific responsibilities to individuals with whom they are in close or indebted relationships (Beauchamp & Childress, 2001). They utilized a model that argues that one party (X) has an obligation of beneficence to another specified party (Y) when the following conditions are met: (a) Y risks loss or damage to life, health or another major interest; (b) X's action is needed, alone or in concert with others, to prevent this loss or damage; (c) X's action is highly likely to prevent this; (d) X's action does not present significant risks, costs or burdens to X; and (e) benefits to Y outweigh harms, costs or burdens X will incur. On this model of beneficence, if all the criteria are met, there is an obligation to assist, but if they are not, there is no obligation even while it remains morally praiseworthy to perform the beneficent action (Stobie & Slack, 2010).

These commentators attempted to apply these conditions to the issue of ART access for HIV-infected participants in vaccine trials. In one scenario (of no access to ART in the surrounds) where party X is a sponsor from a resourced setting and party Y a participant they proposed the following: (a) HIV infection gives rise to a high level of suffering; (b) participants are dependent on researchers to provide ART for them; (c) such treatment would prolong life and allow a higher quality of life; (d) sponsors and researchers can finance the purchasing of ARVs and (e) these costs are outweighed by benefits to infected participants (ibid). They asserted that in this scenario, all the criteria which render beneficence a duty can be met, however, they conceded that if any of these points were to be different, beneficence would *not* be an obligation. If, for example, purchasing ARVs formed a disproportionate amount of the trial budget then point d) could not be met and the beneficent action (to provide ARVs) is no longer obligatory (Stobie & Slack, 2010). In another scenario (ART programs are available but weak) they proposed that (a) HIV infection entails suffering; (b) participants are dependent on researchers to refer them for ART and undertake capacity-building at referral sites (c) this response ranks highly among the interventions offsetting suffering and death; and (d) costs to sponsor-investigators of this response are not so demanding that they imperil the trial (Stobie & Slack, 2010).

In general, these authors argued that to apply an account of specific beneficence to the problem of ARVs in HIV prevention trials, investigators must consider the most appropriate context-dependent response and consider if the costs of the response can be borne (Stobie & Slack, 2010). However, these authors conceded that on this account there are many treatment components for HIV (and not just ART), there are many medical needs participants may present with (not merely HIV), and there are many moderately-costly responses that may assist participants (not merely health-care responses). Therefore, they conceded that duties of beneficence need to be more appropriately limited and specified in order to justify researchers care responsibilities in trials (Stobie & Slack, 2010). Other commentators agreed that beneficence-based accounts would need to be better specified to provide clearer direction to trial stakeholders (Richardson, 2008; Schüklenk, 2010).

Still others have argued for approaches to treatment-access that rest on the duty to rescue others. Ulrich (2011) argued that the duty of rescue creates a basis for researchers to address participants' needs because all people are obliged to help other persons in need 'when no-one else can help and aid can be provided without serious risk to the rescuer' (p. 30). On such accounts, the focus is on needs addressed by relatively simple or cheap interventions (cf. Richardson, 2012a) where responses do not present serious sacrifice to the rescuer (Merritt, 2011) or where they present only minimal burden (Rulli & Millum, 2014). Put another way, underpinning care responsibilities with duty of rescue restricts responses to easily-provided interventions (Richardson, 2012a) and cannot ground complicated steps (Richardson & Cho, 2012). It has also been argued that duty of rescue naturally extends beyond trial participants and taking it seriously would mean addressing needs of everyone in the surrounds, capacity permitting (Richardson, 2012a). It has also been argued that duty of rescue attaches to anyone who can help (Merritt, 2011; Rulli & Millum, 2014), does not set out what is ethically required by researchers in particular (Dickert & Wendler, 2009) and is generally insensitive to any relationship between the rescuer and the person needing rescue (Richardson & Cho, 2012) or transactions between them (Richardson, 2012b).

The debate about what best grounds researchers' responsibilities has been long and complex but, in parallel, discussions have occurred about pragmatic mechanisms to ensure participant access to HIV treatment (Forbes, 2006). In the absence of national working ART programs, some networks and sponsors made plans for alternative mechanisms such as funding set-asides or insurance schemes (BMGF, 2005; GCM, 2005; GCM, 2008; Tucker & Slack, 2003). The HVTN – a clinical trials network funded by the National Institutes of Health – as well as the International AIDS Vaccine Initiative – both committed themselves to funding the provision of ARVs in the event that ARVs were not available in low-resource settings (Fitzgerald, Pape, Wasserheit, Counts & Corey, 2003; IAVI, 2005; WHO/UNAIDS, 2004) for a specified time period or until national programs could provide coverage.

As ART became more widely available in host countries and communities, it was recommended that sponsor-investigators collaborate with treatment-providers (Macklin, 2006a), partner with treatment programs and providers (Macklin, 2008; Tarantola et al., 2007), link with locations where ART is scaled up (Macklin, 2010a) and cooperate with expansion efforts (GCM, 2005). The mechanisms discussed above (funding set-asides or insurance schemes) came to be considered important back-up plans, with the primary goal to

rely on local coverage and to retain the other mechanisms as safety nets (BMGF, 2005) or as bridges until national programs could provide coverage (IAS, 2005; Warren, 2006).

Commentators have long questioned whether responses implemented for participants but not for non-participants might constitute an 'undue inducement' (Guenter et al., 2000; SA MRC, 1998; UNAIDS, 2000a) or undue incentivization (Hooper, 2010) for participants to enrol in trials, although definitions of what constituted undue inducement varied. Some questioned whether treatment-access should be emphasized in discussions with potential participants (Grady et al., 2008). Others questioned whether providing care might attract people who are 'disproportionately predisposed to accessing the full menu' of care services resulting in a skewed selection of participants (Richards & Helmchen, 2012, p. 3).

Others questioned whether it was fair to take steps for participants but not for non-participants thereby introducing disparities between members of the same community (MacQueen et al., 2004; Slack et al., 2005). More specifically, it was argued that taking dedicated steps for participants but not for others constitutes a form of preferential treatment (IAS, 2005) or 'individual attention' that creates inequities 'between neighbours who face similar problems' (Lo, Padian & Barnes, 2007, p. 1230) leading to intra-community tensions (Participants, 2013).

Still others questioned whether the narrow focus on ART might lead to a 'losing sight' of the 'plethora of unfulfilled needs' that participants have, such as needs for reliable contraception and other sexual and reproductive health needs (GCM, 2005, p. 48) as well as more general ailments. Commentators called for an expanded focus on other health needs (BMGF, 2005) and increased attention to the full range of health needs affecting participants (Heise et al., 2008).

From the review above, many ethics commentators have attempted to sketch out the most relevant ethical justifications for *why* researchers should address care needs in HIV vaccine trials (for example, because of standard of care, or because of broad ethical principles) and these commentators did not necessarily agree on the most appropriate justification. It appears that how responsibilities are grounded has important implications for *who* should be the focus of researchers attention (trial participants or others?) or *what* care needs should be the focus of researchers attention (HIV or other needs?) and *what responses* should be

implemented. Despite this, it seems clear that many commentators agreed that arguments existed for researchers so-called positive duties, that is, for taking active steps to promote welfare as opposed to merely refraining from inflicting harm (cf. Merritt, Taylor & Mullany, 2010; Participants, 2008; Richardson, 2012c).

#### 2.3.4 MODELS OF ANCILLARY CARE

The care debate in HIV vaccine trials specifically, and other HIV prevention trials, was conducted in parallel with a broader debate in the research ethics literature about how best to conceptualise the responsibilities of sponsor-investigators to address participants' care needs in medical studies more generally (Belsky & Richardson, 2004; Merritt, 2011; Participants, 2008; Richardson & Belsky, 2004; Richardson, 2007) especially those conducted in low-resource settings (Olson, 2014). That is, it occurred alongside a broader debate about sponsor-investigators obligations to address participants' health-care needs in studies where researchers could not rely on more familiar reasons to address these needs, such as care is required for the scientific success of the trial, or care is required to keep participants safe or care is required to redress trial-injuries (Belsky & Richardson, 2004).

Addressing needs when the possible reasons for doing so fall outside well-accepted justifications, such as scientific necessity or safety, has come to be termed 'ancillary care' (Belsky & Richardson, 2004). The term 'ancillary' denotes that the rationale for addressing the need falls between the cracks of more familiar rationales, such as science or safety. Ancillary care may be needed for the condition under study, or for other conditions identified by tests in the trial, or for conditions that are entirely unrelated to either the study question or study procedures (Dickert & Wendler, 2009). Put simply, the term refers to care where the grounds for *providing it* are not research-related (Richardson, 2012c). It is recognized that ancillary care may inadvertently strengthen the science by, for example, improving retention but so-called 'soft science' reasons are not the primary grounds for such responses (Richardson, 2012c).

#### 2.3.4.1 THE PARTIAL ENTRUSTMENT ACCOUNT OF ANCILLARY CARE

It has been argued that many of the previous arguments about sponsor-investigators' care responsibilities that are based on ethical principles are somewhat unfocussed. For example, it has been argued that beneficence-based arguments are 'undifferentiated' (Richardson, 2008, p. 257). It has been asserted that duties of rescue applies to *all persons* (not just researchers) and apply when the need is dire and the needed intervention is comparatively simple, low-risk, or inexpensive to provide (Hawkins, 2008; Merritt, Taylor & Mullany, 2010; Richardson, 2008) - the so-called 'easy fix' (Merritt, 2011, p. 322). Some argued that researchers do not bear a special responsibility to remedy injustices that they did not cause (Dickert & Wendler, 2009). It has been noted that there has been inadequate justification for the obligations of researchers *in particular* to the health-care needs of participants (Participants, 2008) and inadequate justification for the claims that researchers *in particular* have a special obligation to address care needs (Richardson, 2008) – especially to provide more complex, lengthy or costly responses that go beyond what would be called for by duties of rescue (Richardson, 2009a; Richardson, 2012).

It has been argued that a sound justification for the obligations of researchers to address participants' care needs lies in the relationship between researcher and participant, and from the transactions between them (Richardson, 2009b). Some commentators argued that the care debate has been characterised by extreme polar representations of researcher-participant relationship. On the one hand, researchers have been viewed as pure physicians (Richardson & Belsky, 2004) with a 'therapeutic obligation' (Miller & Brody, 2003, p. 24) where researchers' care obligations are seen to extend very broadly to all aspects of participants' health (Richardson, 2008). On the other hand, researchers have been viewed as pure scientists, where they are seen to have few care obligations (Richardson & Belsky, 2004) but rather obligations to implement the scientific protocol (Haire, 2012) or make decisions out of concern for the scientific design of the study (Rangel, 2010).

It has been argued that the most appropriate characterization of the relationship between researchers and participants lies somewhere in the middle, and is a relationship of partial entrustment (Richardson & Belsky, 2004). More specifically, that is, participants 'entrust' to

researchers a narrow subset of their health by granting express permissions for researchers to conduct specific trial procedures (for example, tests, blood draws) and that researchers come to accept responsibility to respond professionally to this specific medical information through their specialised skills and training (Richardson & Belsky, 2004).

Richardson (2008) set out that participants provide permission for researchers to do otherwise-impermissible things, such as to touch participants in certain ways, to collect tissue samples or bodily fluids, and to collect medical information about them that would otherwise be confidential. He argued that by soliciting these permissions, researchers implicitly agree to receive this private information and accordingly become entrusted with special responsibilities pertaining to this information, namely to respond appropriately and professionally (Richardson, 2008). That is, he argued that researchers have *special responsibilities* to research participants by virtue of their professional role (Richardson, 2008). These entrustment-based obligations exist in addition to, or as a supplement to, or 'over and above any more general positive obligations' that are incumbent on any person (Richardson, 2008, p. 261; Richardson, 2012c). It was argued that this special responsibility is the core of researchers' ancillary-care obligations (ibid).

On this account, researchers have special entrustment-based responsibilities to consider care for medical conditions identified by trial procedures (Richardson, 2007). Such conditions are considered to fall within 'scope' (Belsky & Richardson, 2004). These conditions may be of varying degrees of scientific importance to the study (more below) but on this account all conditions identified by modes of information-gathering in the research generate potential entrustment-based claims for care. One of this model's distinct contributions is to move beyond considering care only for conditions that are important to the study, such as trial endpoints (Participants, 2008). On this account, given aspects of participants' health are considered to be entrusted to the researchers - and so to be within the scope of entrustment-based obligations - if researchers needed permission to collect information about them in order to proceed with their study (Richardson, 2008) or had to secure a privacy waiver from participants to identify them (Merritt, 2011). Proponents of the entrustment model therefore recognise the distinction between needs identified via research-related interaction versus needs identified by mere casual observation (Taylor et al., 2011).

Richardson (2007) asserted that a condition may be *centrally* within scope – that is it is very important to the research (for example, it constitutes the study endpoints) or *clearly* within scope, that is, it is a condition that is important to the study design but is not an endpoint or *minimally* within scope (that is, it is not important to the study). The model’s proponents have been careful to point out that all entrusted conditions generate potential claims to care and the endpoint is not necessarily privileged (cf. Participants, 2008). However, it has been implied that when a condition falls centrally in scope (and is important to the research) then this impacts on the strictness of the obligation to address it (cf. Richardson, 2007). For example, the obligation to ‘provide’ care for HIV in an HIV vaccine trial was seen to rest in part on the notion that HIV status is central to the research and that HIV acquisitions are scientifically important to the research (Richardson, 2007, p. 1960). On this account, however, the responsibilities of sponsor-researchers are not restricted to, or centered on, addressing target conditions (Participants, 2008, p. 0709). It is recognised that many needs will be encountered through study procedures (Participants, 2008). This model’s dissemination has coincided with increasing recognition that participants in HIV prevention trials present with multiple health threats – unintended pregnancies, STIs or other health needs (MacQueen & May, 2008) including anemia, hypertension and others (Ramjee et al., 2010).

On this account, when a condition is identified by a trial procedure (or falls within scope) it means that participants have a potential claim that *researchers should address* their care need. Researchers need to consider a series of moral factors (discussed below) to assess the strength of this claim (Belsky & Richardson, 2004) and establish the strength of researcher responsibilities to address the ancillary care needs they identify (Participants, 2008). When the strength of these factors is considered ‘high’, then there is a strong claim that researchers must respond to the care need (Richardson, 2008) and ‘see to it that the person receives adequate care addressing that need’ (Richardson, 2008, p. 260). On this account, a test of strength must be satisfied, and if it can, the researchers who generated the finding have some obligation to *see to it* that the research participant gets appropriate care (Richardson, 2008, italics mine). It has been observed that the ‘appropriate moral response’ might ‘look quite different’ depending on the context (Richardson, 2008, p. 260) and that a wide range of responses is possible (Richardson, 2012c). But first, it would help to consider the factors

considered relevant to working out the strength of a participant's claim that researchers address their need – including, gratitude, engagement and vulnerability (Richardson, 2007).

More specifically, the factor of *gratitude* is assessed by considering the uncompensated risks and burdens assumed by participants (Belsky & Richardson, 2004) or their undergoing of procedures that may be risky, painful or inconvenient (Richardson, 2008). The factor of *engagement* is assessed by considering the depth of the relationship between researcher and participant based on the length (Belsky & Richardson, 2004) and intensity (Richardson, 2007; Richardson, 2008) and extensiveness of the proposed interactions between researchers and study participants (Participants, 2008) that can be expected on the basis of the protocol (Richardson, 2007; 2008). Engagement or depth can be minimal (for example, screening protocols where persons undergo some procedures to establish their eligibility); low (for example, studies where there are a few brief interactions); medium (for example, studies where there are many interactions over a number of years; and high (for example, studies with many follow up visits and intensive monitoring) (Richardson, 2007). It is asserted that when the relationship is deeper, researchers have a stronger moral responsibility to engage with participants' needs (Belsky & Richardson, 2004). The factor of *vulnerability* is assessed by considering how badly off participants would be if they did not receive help (Richardson, 2007), how much difference getting care would make to their health and welfare (Richardson 2008) or how severe/ acute the need is and what would be the consequences were the need to go unmet (Participants, 2008).

The model's proponents asserted that the appropriate response will depend on the context (Richardson, 2008) and that gradations of responses are possible (Richardson, 2007). Merritt (2011) acknowledges that the possible range of responses extends from doing nothing to address the need, on the one hand, to making it one's most urgent priority, on the other hand. She asserts that the core issue is identifying – from all the options – those actions researchers must take (Merritt, 2011). On the partial entrustment account, researchers must assess the context, namely what alternatives are available such as the existing health-care system or other health-care opportunities and whether the identified need can be met by these alternatives bearing in mind possible constraints on infrastructure and personnel. Where participants have a strong claim to care based on gratitude, engagement and

vulnerability, then *even fairly demanding responses* (such as direct provision of care) must be entertained (Joseph Millum, personal communication, June 2011). However, the model acknowledges that there must be limits on potential responses – a so-called ‘threshold of costliness’ (Richardson, 2012, p. 407) to prevent them from becoming ‘relentlessly demanding’ (Merritt, 2011, p. 321).

More specifically, decision-makers must assess the ‘costs’ of the response which can be considered low (negligible), serious or heavy in relation to the overall budget (Richardson, 2012c). Costs in terms of financial resources (money) as well as costs of human resources (personnel) in terms of diverting study staff must also be considered. Costs related to confounding study results (Belsky & Richardson, 2004), undermining study power (Richardson, 2007), or interfering with the study’s scientific aims must also be considered. On this account it appears that where the response will not overwhelm the study (Merritt, 2011) nor overwhelm the study activities (Richardson, 2012) nor seriously distract researchers from their core work (Richardson, 2009b) nor confound the science then the response should be implemented. Merritt (2011) acknowledged that it is a matter of judgment to determine whether the costs of various responses will be acceptable or inordinate, and to establish a ‘principled cut-off’ between acceptable and excessive costs (p. 342).

This account does recognise however that responsibilities to implement extra-scientific responses, or ancillary-care responses are not unbounded and this account respects the central goal of research (generating generalizable knowledge) as a valuable one (Rangel, 2010). This account allows, therefore, that responsibilities to their scientific mission (and benefitting a future collective) may legitimately limit researchers’ ancillary-care responses to participants (Richardson, 2009b). As such, ancillary-care responses do not necessarily comprise ‘unrestrained obligations’ (Richards & Helmchen, 2012, p. 2).

This framework has been expressly applied to the issue of HIV vaccine trial participants needing ART in a context where it is not accessible in the community (Richardson, 2007). Richardson (2008) observed that HIV vaccine trials introduced a difficult ethical question, namely: ‘do the researchers or their sponsors have any obligation to help secure ART for trial participants who become HIV-positive during the course of the trial?’ (p. 257). Richardson

(2008) noted that such treatment for HIV vaccine trial participants falls into the definition of ancillary care because it is care that participants need, but is not covered by a previous rationale such as safety or promise, or compensation and providing ART does not contribute to the scientific aims of the trial.

Richardson (2007) applied this framework to HIV vaccine trials to provide a way to work out the comparative strictness of researchers' obligations to provide ART (viewed as a type of ancillary care) while acknowledging the range of potential responses (Richardson, 2007). It was noted that HIV falls into the scope of investigators' moral concern because HIV is explicitly diagnosed in such trials from a special authorization granted by participants (Richardson, 2007) and furthermore that HIV falls centrally within scope because tracking participants' HIV status is central to the study (Richardson, 2008). It was argued that the strength of the investigators' entrustment-based obligation to provide ART would be heightened by the fairly long interaction required by phase III HIV vaccine trials (engagement); the number of risks and burdens assumed by participants (gratitude); the suffering should HIV go untreated (vulnerability); and the few reasons against providing care in this case because the costs of providing ART in phase III trials were judged to form a low proportion of the overall trial budget (Richardson, 2007). It has been claimed that all the factors impacting researchers' care responsibilities can be examined at the early stage of protocol review on the basis of the study design (Richardson, 2008) and that RECs are a natural venue for consideration of such issues (Richardson, 2009b).

#### 2.3.4.2 THE WHOLE PERSON ACCOUNT OF ANCILLARY CARE

It has been argued that the partial entrustment account of ancillary-care responsibilities is the most systematic account yet proposed (Dickert & Wendler, 2009). Critics have agreed that ancillary-care responsibilities are rooted in the researcher-participant relationship (Dickert & Wendler, 2009) and are largely delimited by the nature of the researcher-participant relationship (Dickert et al., 2007) however they have argued that it is restrictive to limit potential claims to care to needs identified by *study procedures* and perhaps inappropriate to consider the relatedness of the need to the *study question* (Dickert & Wendler, 2009, Dickert,

2009). They have acknowledged nonetheless that these considerations seem a straightforward way to bound responsibilities (Dickert, 2009).

More specifically, these critics noted that two participants may have engaged in the same intense relationship with researchers, may have assumed the same risks or burdens, and may have needs that present similar costliness of response. However if one participant's condition is identified through a 'basic interaction' (such as being observed by the naked eye in the corridor) and another participants' condition is identified via a *study procedure* then the former would fall outside the scope of entrustment, and investigators would have no responsibility to provide care on the partial entrustment account (Dickert & Wendler, 2009, p. 426). They argued that this seems to omit something critical about the relationship between researchers and participants (Dickert & Wendler, 2009).

More specifically, they argued that the relationship should not necessarily be determined by the subset of needs entrusted (Dickert et al, 2007), that the relationship is not defined by study procedures and questions (Dickert & Wendler, 2009) and that 'there is more to this relation than what is entrusted' (Dickert et al., 2007, p. 875). They recalled that Belsky and Richardson (2004) suggested that the researcher-participant relationship involves 'engaging with whole persons and that failure to recognise this represents treating persons merely as a means to generate data' (Dickert & Wendler, 2009, p. 426) and then questioned how such a view could be consistent with the assertion that non-entrusted needs generate no special claim on researchers to address (ibid). Critics also questioned the gradations of scope, wondering whether it matters if the need is important to (or tightly connected to) the *study question* (Dickert et al., 2007) asking whether participants who entrust a condition central to the study (and of more importance to the study) have entrusted more than participants who entrust a condition not central to the study.

These commentators favoured abandoning or dissolving the scope boundary and proposed that a broader range of needs should be eligible for the special duties of researchers (Merritt, 2011). Presumably this broader range of needs might include those identified by casual observation. They were essentially arguing for a 'wider view of scope' (Bright & Nelson, 2012, p. 675) or less restrictive view of scope (Dickert, 2009). These commentators endorsed the

importance of the strength factors outlined by the partial entrustment account - such as gratitude or engagement - but recommended more attention to those factors that vary by condition (such as vulnerability) and reasons against care, such as expense, simplicity, feasibility, and site-staff expertise (Dickert & Wendler, 2009). They acknowledged that all the strength factors are relevant and one should not necessarily be allowed to 'hijack' or 'trump' all the other considerations (Dickert et al., 2007, p. 877).

They agreed with the view that the relationship is influenced by whether it involves significant risk or sacrifice or is deeply personal and persists over time (Dickert, 2009). They agree that researchers are obligated to do more for those participants with whom they work closely or over a long period of time, or whom have absorbed a greater amount of uncompensated risk and burden (Dickert & Wendler, 2009). They agreed that the strength of the responsibility to address needs increases as 'the investigator-participant relationship deepens through more involved interactions, procedures, or repeated visits' (p. 427). However they proposed that these strength factors influence whether researchers should address even those needs unrelated to the study question or study procedures. Their approach has come to be termed the whole-person account (cf. Merritt, 2011).

They agreed there are ranges of possible ancillary care responses, such as informing participants about their condition, providing referrals, paying for treatment, and providing treatment (Dickert & Wendler, 2009). They agreed that there are limits to such responses for example where the costs of a response 'outstrip' budgets or 'jeopardize' studies (p. 425) or 'overwhelm' research (p. 427) asserting that care obligations should not 'fulfilled at the expense of good science' (p. 427). Like the partial entrustment account, the whole person account recognises that researchers can prioritize the interests of participants over the interests of the general population (Merritt, 2011) even while proponents of the whole person account do reference fairness concerns if participants receive care while non-participants do not (Dickert & Wendler, 2009). Like proponents of partial entrustment, these commentators recommended that the types of care responses to be implemented should be specified for RECs (Dickert & Wendler, 2009). They also recognised that the role of host communities in determining which needs are met remains somewhat unaddressed (ibid). It has been

asserted that the partial entrustment and whole person accounts are two of the most developed and leading accounts of ancillary care (Merritt, 2011).

#### 2.3.4.3 THE FOUR P'S ACCOUNT OF ANCILLARY CARE

A popular account of ancillary care has also been developed – termed the Four P's. This account was developed to assist stakeholders to determine ancillary-care responsibilities without requiring them to subscribe to the partial entrustment-based view but rather resting on some positive obligation. Therefore on the Four P's account it is less important how needs are identified and this account merely encourages researchers to consider what *needs* might be encountered (either by study procedures or because of their prevalence in the community).

It encourages stakeholders to consider how strong is the responsibility of researchers and sponsors to address the ancillary-care needs they identify in studies based on answers to questions such as what is the study length and extensiveness of researcher-participant interactions; and how severe are the care needs and what would be the consequences if the need were to go unmet? (Participants, 2008). On this account, where responsibilities to address needs are considered to be high, researchers have a *positive duty* to take definite practical, *pragmatic steps* to address needs. Researchers need to develop *plans* for how they will respond to participants' care needs. Some of the pragmatic steps researchers can take towards meeting their obligations include budgeting appropriately, hiring medical personnel, and *partnering* with treatment providers (Participants, 2008).

Proponents of the Four P's have recommended that sponsors develop plans for their general approach to ancillary care. They should also develop plans in each protocol for addressing care needs (predictable and not). They should pre-emptively cost out ancillary-care responses. The model's proponents have argued that planned steps to address needs should be outlined or stated in protocols so that RECs can review these as an integral part of their review (Participants, 2008). The model has argued that RECs are well situated to judge specific local factors that count in ancillary care (Participants, 2008) and to insist on advance

planning for addressing ancillary-care needs (Richardson, 2012c). It is also recommended that such committees consider the sponsor's identity and ability to support ancillary care. It has been asserted that studies (and study context) will differ in ways that impact on care responsibilities therefore a 'protocol by protocol review is essential' (Participants, 2008, p. 0712). Recognizing ancillary-care responsibilities therefore calls for 'detailed descriptions of expected services' in protocols (Richards & Helmchen, 2012, p. 3) and there have been calls for RECs to be empowered to consider ancillary-care issues when reviewing protocols (Tshikala, Mupenda, Dimany, Malonga, Ilunga & Rennie, 2012).

Concerns have been voiced that the implementation of ancillary-care frameworks will be demanding for stakeholders (cf. Participants, 2008). For example, researchers and reviewers need to predict the conditions that may be uncovered by researchers, and assess alternatives available for the array of care components (drug regimes, psychosocial care) for such conditions in the surrounds of multiple sites then plan their responses and attendant costs.

### 2.3.5 **COMMUNITY ENGAGEMENT**

There has also been debate regarding the specific role that participating communities should play in care-related issues in HIV vaccine trials (MacQueen & Sugarman, 2003) even while endorsing more broadly that engaging community in care-related issues is critical (Heise et al., 2008; MacQueen & May, 2008; Participants, 2008). Some commentators have argued that the best foundation to ground the practice of providing treatment to those who acquire HIV-infection in prevention trials lies in moral negotiation with participating communities (Weijer & LeBlanc, 2006). They asserted that the basis of moral negotiation lies in the principle of respect for communities which they interpret as taking seriously community values and respecting decisions of 'legitimate communal authorities' (Weijer & LeBlanc, 2006, p. 805). Weijer and LeBlanc (2006) have argued that respect for communities can be specified in a number of ways, including consulting community members to ensure the research addresses local health needs and priorities.

Importantly, such specification (on their account) also includes allowing communities 'to

identify benefits that are consistent with their own health-related priorities' and are deemed valuable, including care (Weijer & LeBlanc, 2006, p. 804/805). On their recommendation, there should be a dialogue with communities about research benefits to ensure that benefits are 'consistent with communal health-related priorities' (p. 807). More specifically, communities and researchers should negotiate benefits associated with trial participation, allowing differing solutions to arise for different communities (Weijer & LeBlanc, 2006). They asserted that in a community without access to basic health care for its members (or even clean water), ART for infected trial participants may not be a high priority and the community may prefer help to establish a clinic to address general or basic needs of community members (or even a well for clean water). However, they allowed that, in another community, access to ART for participants may be deemed the highest priority by participating communities.

Other commentators have also proposed that, in order to define treatment responsibilities in vaccine trials, researchers should engage stakeholders, including community representatives, in a structured decision-making process, to allow agreement to be reached on core obligations regarding care (Tarantola et al., 2007). This approach has been termed the 'good governance' approach. These authors proposed that stakeholders must consider who gets care (screen-outs? trial participants? community members?) and for what (the target disease? other conditions identified in the trial?). However this model offers little guidance on which substantive moral rationales will carry the day in working out these difficult questions, and merely proposed that stakeholders must consider important ethical norms in their deliberations.

It has also been recommended that a study's package of ancillary care should be defined after a 'locally-driven deliberative process among concerned stakeholders' to elucidate their preferences (Hyder & Merritt, 2009, p. 430). Some commentators have recommended that communities should engage in a process of bargaining with, or negotiating with, researchers for a wide range of benefits, including care (Participants, 2004). This so-called 'fair benefits' approach aims to respect the autonomy of host communities, and facilitate free decision-making. This approach also aims to assist research stakeholders to reach outcomes that are fair, ensuring that participating communities are not exploited (London & Zollman, 2010). Proponents of this approach argued that exploitation is best avoided by ensuring that people

who assume the research burdens receive fair benefits, more specifically that 'benefits should correspond to burdens, benefits to others and relative contributions' (London & Zollman, 2010, p. 37). One of the recommended criteria for fair benefits was the provision of collateral health services to participants or participating community - health services beyond those required for conduct of the research (Participants, 2004). Therefore on the fair benefits approach, access to ancillary care (care not required for science or safety) was considered to be one possible benefit that host communities could negotiate with researchers. Even accounts based on rectifying social inequalities between sponsor and host countries have recommended consultation with the community to identify the needs and care elements most important to the host population (Shapiro & Benatar, 2005).

Critics of the fair benefits approach have argued that it does not set out the relationship between a process of negotiation, on the one hand, and its claims about what constitutes fair benefits, on the other hand (London & Zollman, 2010). Critics have argued that sometimes the fair benefits approach sounds like a pure procedural approach where an outcome is regarded as fair when it is produced by a particular procedure and when outcomes that do not satisfy certain substantive conditions still count as fair as long as all parties accept them. Critics argue that at other times it sounds like an imperfect procedural approach where there are some restrictions on the outcomes considered acceptable, and where outcomes are considered fair 'according to some independent standard or criterion of fairness' (London & Zollman, 2010, p. 42).

Critics argued that if the fair benefits approach is an imperfect procedural approach, then fair-benefits proponents must provide an account of how host communities should negotiate with researchers so that resulting bargains satisfy certain substantive conditions of fairness (London & Zollman, 2010). It has been asserted that unless the fair benefits approach is better specified, then it is possible it results in a 'race to the bottom' (London & Zollman, 2010, p. 41) where communities compete against each other by trying to make themselves more appealing hosts by lowering their costs, and where investigators are tempted to locate their research projects in communities with the lowest costs. Others have questioned whether communities could ever have equal bargaining power with sponsor-investigators that would enable them to negotiate a fair amount of the benefits (Schüklenk, 2010) and that

negotiations run the risk that outcomes are determined by the opinions of the majority or the most powerful or the loudest (Stobie & Slack, 2010).

### 2.3.6 SUMMARY OF THE ACCESS TO CARE DEBATE

In summary, this part of the review indicates that there has been an intense debate about researchers' responsibilities to respond to the medical needs of participants in trials, with emergent arguments grounded in standard of care, or broad ethical principles or new ethical frameworks. The original debate was initially focussed on HIV, and focussed on researchers' obligations to secure access to ART for participants in settings where it was not routinely available. In more recent years, as ART has become more available in resource-poor settings, and possibly as influential ancillary-care accounts have been published, there has been a shift towards focussing on other components of HIV care and other needs identified in trials (not merely care for the trial end-point) (Shapiro & Benatar, 2005; MacQueen & May, 2008). There has also been debate about the appropriate recipients of ancillary-care responses, and the limits that should be placed in ancillary-care responses (Merritt, 2011). The reasons that researchers have responsibilities (Merritt, 2011), or the source of their obligations (Tarantola et al., 2007), remains a source of debate.

To date there has been little effort to explore how vaccine stakeholders at the coal face of ancillary-care responses themselves personally understand or frame ancillary-care responsibilities. While such data might not settle arguments about the most convincing account, it would illuminate which arguments stakeholders themselves find most convincing. There has also been little work characterising the 'positive, helping performances' (cf. Richardson, 2012c, p. 206) being implemented in HIV vaccine trials specifically, and characterising the contemporary problems or issues that are most pressing for stakeholders.

This part of the review also shows that there have been various proposed approaches to community engagement such as moral negotiation approaches. Critics have, in particular, questioned recommendations that participating-community representatives should negotiate with researchers, for example, questioning their real bargaining power. To date,

there has been limited exploration of the experiences of vaccine stakeholders involved in researcher-community interactions at trial sites, and the concerns they personally experience when engaged in care-related interactions.

## **2.4 RECOMMENDATIONS IN ETHICAL GUIDELINES**

Ethical guidelines currently set out many recommendations that are relevant to this debate. Some general ethical guidelines (CIOMS, 2002; WMA, 2013) are briefly reviewed first, followed by more specialized ethical guidelines for HIV prevention trials (SA MRC, 2003; UNAIDS/WHO, 2007; 2012; UNAIDS/AVAC, 2011).

### **2.4.1 GUIDANCE NOT SPECIFIC TO SOUTH AFRICAN HIV VACCINE TRIALS**

The Declaration of Helsinki (WMA, 2008; 2013) asserts that physicians have a duty to protect the life and health of patients including research participants. This has led to two interpretations. Specifically a strong interpretation where it is held to mean that researchers must provide care for diseases that threaten the health of their participants (Tarantola et al., 2007) which has been criticized as placing unreasonably expansive obligations on researchers (Participants, 2008). It has also had a weaker interpretation that researchers must merely minimize research-related risks, take steps to prevent research-related harms, and provide treatment for adverse events (Tarantola et al., 2007).

CIOMS (2002) asserts that ancillary care responsibilities are non-obligatory but are rather morally praiseworthy or supererogatory (CIOMS, 2002; Pratt et al., 2013; Stobie & Slack, 2010). More specifically, CIOMS (2002) asserts that sponsors only have an obligation to provide health-care services if the services are essential to scientific or safe conduct of research, or constitute treatment for injury, or are explicitly agreed to, or are part of post-trial availability commitments - all other instances of service-provision would be morally praiseworthy.

The Nuffield Council on Bioethics (NCOB, 2002) asserts that participants in prevention trials who develop the disease that is the target of the preventive intervention should be offered a universal standard of care but where this is 'not appropriate' they should be offered the best available intervention as part of the national public health system for that disease (p. 96). For participants in prevention trials who develop diseases unrelated to the target condition, they should be offered the best intervention available as part of the national public health system.

Local guidelines for health research in South Africa do not deal in much detail with the explicit issue of ancillary care. One guideline that provides general guidance for researchers funded by the Medical Research Council (SA MRC, 2002) asserts that participants in international collaborative research should be provided with care and treatment that they would not normally get – implying at first glance that researchers reject the local *de facto* standard of medical services for participants and take steps to help participants secure improved care. However, this short statement is somewhat ambiguous because it is conceivable that participants could be provided with care and treatment they would not normally obtain merely through their involvement in procedures intended to promote the science or safety of trials (for example, better monitoring for adverse events).

National guidelines for all health research conducted in South Africa (SA DOH, 2004) assert that in multinational collaborative research, developed-country participants should not be offered better standards of care than South African study participants, even while criticizing a narrow focus on equivalent drug regimens in standard of care debates and acknowledging that it may not be possible to have equivalency between settings in all components (care facilities, technology). These guidelines suggest that 'researchers from highly resourced countries bear some responsibility to promote better health care and research conditions by garnering additional support from partners in their own countries' and 'to improve the often deplorable conditions' in host countries (p. 8). Guidelines for good clinical practice (SA GCP, 2006) merely assert that the principal investigator should inform participants when they become aware that medical care is needed for inter-current illnesses.

Many recommendations on the explicit issue of ancillary care exist in international ethical guidelines specifically for HIV prevention trials (UNAIDS/WHO, 2007) which were updated with an additional guidance point on intravenous drug users in 2012 (UNAIDS/WHO, 2012); as well as international guidelines for stakeholder engagement in HIV prevention trials (UNAIDS/AVAC, 2011). Guidance also exists in ethical guidelines for HIV vaccine trials in specific countries such as South Africa (SA MRC, 2003). There are also recommendations in ethical guidelines for specific prevention trial networks (HPTN, 2009) which are reviewed briefly before a fuller review of guidance impacting directly on South African HIV vaccine trials.

The guidelines governing researchers affiliated with the HIV Prevention Trials Network (HPTN, 2009) recommend that trial participants have access to care for HIV and sexual and reproductive health needs. Sponsor-investigators should take various steps for care such as reviewing relevant health needs and available services and partnering with local institutions. These guidelines appear to recommend the partial entrustment model of ancillary care, and set out familiar factors from that model for researchers making decisions about ancillary-care responses. More specifically they recommend that researchers consider the factors of vulnerability, engagement, gratitude for risks and burdens, as well as the costs of various responses. They also assert that researchers must provide at the very least equally adequate care services to those in the local community, and seek to enhance standards of care in the local community where they are low by capacity-building. They recommend that stakeholders should strive to provide ART for participants acquiring HIV during the course of trials, but where there is a plan to improve local services, a lack of ART to sero-convertors is permissible. The guidance recommends that participants should understand different kinds of care they will get (care related to the study versus purely to benefit them) and information about care should be reviewed by review bodies. Communities should be consulted to help anticipate the ancillary-care needs of participants and to decide on care, and stakeholders should reach consensus on care.

#### 2.4.2 GUIDANCE SPECIFIC TO SOUTH AFRICAN HIV VACCINE TRIALS

In this next section, a close reading is undertaken of the three ethical guidelines that bear directly on South African HIV vaccine stakeholders, namely: *Guidelines for medical research: HIV preventive vaccine trials* (SA MRC, 2003); *Ethical Considerations in biomedical HIV prevention trials* (UNAIDS/WHO, 2007; 2012) and the *Good Participatory Practice Guidelines for biomedical HIV prevention trials* (UNAIDS/AVAC, 2011). Recommendations in these ethical guidelines have been collated to provide an overview of ethical direction currently provided to stakeholders in the field on various concerns. It is worth noting that the SA MRC (2003) guidelines were endorsed by the National Health Research Ethics Council as setting the standard for all HIV vaccine trials in the country, regardless of the researchers' affiliation.

These guidelines make various recommendations including about sponsor/investigator responsibilities to various groups such as enrolled participants, volunteers who present for screening and participating communities; about HIV needs specifically as well as sexual and reproductive health needs and general needs more broadly; about responses to be implemented to address needs; about what protocols should say; and about how participating community representatives should be involved. These ethical guidelines tend to adopt a particular approach to influencing the conduct, actions or practices of vaccine stakeholders, namely exhorting stakeholders to adopt certain practices versus prescribing or mandating the same (cf. Campbell & Glass, 2001; Chalmers, 1995; Eriksson, Helgesson & Segendahl, 2006). The ethical guidelines assert that they highlight critical elements to be *considered* (SA MRC, 2003; UNAIDS/WHO, 2007; 2012).

These ethical guidelines tend to be aspirational rather than pragmatic (cf. Macklin, 2001a, 2001b; Macklin, 2005). Aspirational guidelines do not rely on past practices to establish guidance but rather set out ideals to strive for, whereas pragmatic guidelines tend to rely on past practices as a guide to what is possible (Macklin, 2001a). It has been argued that aspirational guidelines should represent the ceiling and not the floor, even while avoiding being 'impossibly ideal' or 'hopelessly aspirational' (Macklin, 2001a, p. 23).

These ethical guidelines adopt a blend of content-based or substantive recommendations, as well as procedure-based recommendations (cf. Christakis & Levine, 1995; Levine, 2005). The former set out what should be done whereas the latter set out procedures to follow to comply with the substantive norms or even to work out what to do when substantive recommendations do not give clear direction (Levin, 2005). The ethical guidelines themselves assert that they set standards as well as procedures for arriving at standards (UNAIDS/WHO, 2007; 2012).

The actual impact of such ethical guidelines on practices may, of course, be constrained by various factors including low stakeholder awareness or low understanding or low perceived relevance to contemporary problems. There has been little research exploring awareness and use of such guidelines however one study showed several guidance statements were rated positively by prevention stakeholders on various dimensions (Moorhouse, Slack, Quayle, Essack, & Lindegger, 2014). Another study found many research stakeholders were aware of participatory practice guidelines but fewer had actually read them (Miller, Bass, Warren, Grant, Coestelloe-Kuehn, Fuher, & Fisher, 2009). This suggests that efforts to develop comprehensive and sensitive guidance must be coupled with efforts to ensure their impact.

#### 2.4.2.1 GUIDELINE RECOMMENDATIONS FOR PARTICIPANTS

In terms of participants with **HIV needs**, there is consistency across all three ethical guidelines that participants who become infected with HIV while in trials (despite prevention services being offered) should have access to a package of high quality treatment and care for HIV infection that includes ART (SA MRC, 2003) or have access to treatment regimens from among those internationally recognised optimal, 'including ART' (UNAIDS/WHO, 2007, p. 48) or have access to a comprehensive package of care (access to all preventive, psychosocial, psychological and clinical components of HIV care) and treatment from regimens internationally recognised as optimal (UNAIDS/AVAC, 2011). The recommended package shares consistencies, namely: counselling and referral to social support (SA MRC, 2003; UNAIDS/WHO, 2007; 2012); immune monitoring (SA MRC, 2003); prevention/ treatment of opportunistic infections; TB prevention and treatment (SA MRC, 2003; UNAIDS/WHO, 2007; 2012); ART (SA MRC, 2003; UNAIDS/WHO, 2007; 2012); treatment for other STIs; family

planning (SA MRC, 2003; UNAIDS/WHO, 2007; 2012); reproductive healthcare for pregnancy and childbirth (UNAIDS/WHO, 2007; 2012) and PMTCT (UNAIDS/WHO, 2007; 2012) and home based care and palliative care (SA MRC, 2003; UNAIDS/WHO, 2007; 2012).

The guidelines recommend various steps for researchers addressing participants' HIV needs – they recommend that investigators *integrate* with national treatment plans, *integrate* with local systems (UNAIDS/WHO, 2007; 2012) and modify treatment plans in line with updated *national guidelines* (UNAIDS/AVAC, 2011) which implies that participants' HIV care should be indexed to national treatment norms and guidelines (Slack, 2014). Other guideline-statements recommend that participants in high and low income countries should be 'treated equally' regarding treatment-access (UNAIDS/WHO, 2007, p.48), and the treatment standard should be 'equivalent across high, low and middle-income countries' (UNAIDS/WHO, 2012, p.65) which implies that participants' HIV care should be indexed to international treatment norms and guidelines (Slack, 2014). It appears that the UNAIDS/WHO guidelines endorse that participants' HIV care be anchored to a *de jure* standard – but present two standards for researchers to reach – a national *de jure* standard and a global *de jure* standard.

In terms of participants with **sexual and reproductive health needs** (that is, even for participants who do not acquire HIV infection) ethical recommendations are fairly scattered in the UNAIDS/WHO (2007; 2012) guidelines – which state that participants should get family planning, pregnancy and childbirth services (under a guidance point on prevention), appropriate reproductive and health counselling and services (under a guidance point on women) and access to reproductive health care services (under a guidance point on benefits) (UNAIDS/WHO, 2007; 2012). All the ethical guidelines assert that participants should receive STI treatment, under recommendations for standard of prevention (SA MRC, 2003; UNAIDS/WHO, 2007; 2012, UNAIDS/AVAC, 2011). UNAIDS/AVAC (2011) merely provides sexual and reproductive health care as an example of non-HIV care that could be made available to participants. In terms of **other care** for participants, ethical guidelines make surprisingly few recommendations – merely stating that participants should have regular and supportive contact with healthcare workers and counsellors throughout the trial, under benefits (SA MRC, 2003; UNAIDS/WHO, 2007; 2012) and that protocols should spell out ancillary services that may benefit participants (UNAIDS/WHO, 2007; 2012).

The focus on HIV needs in these ethical guidelines is not at all surprising given the intense debate on this issue that has accompanied the development of guidance (Guenter et al., 2000; Macklin, 2010a; WHO/UNAIDS, 2004). It is clear that ethical guidelines have begun to alert readers that the debate has moved somewhat beyond addressing HIV needs only, and has moved to encompass other health threats (MacQueen, Namey, Chilongozi, Mtwewe, Mlingo, Morar, Reid et al., 2007; MacQueen et al., 2008) or other conditions identified in trials (Belsky & Richardson, 2004; Ngongo et al., 2012; Participants, 2008; Shapiro & Benatar, 2005).

#### 2.4.2.2 GUIDELINE RECOMMENDATIONS FOR NON-PARTICIPANTS

It is recommended that **volunteers with HIV** (namely persons screened out of trials because they are HIV-infected) should be referred to existing health-care services (SA MRC, 2003) or to clinical and support services (UNAIDS/WHO, 2007; 2012). UNAIDS/AVAC (2011) merely states that its provisions on care/treatment for participants (see above) apply to volunteers with HIV, and recommends stakeholders discuss this issue (during protocol development). In terms of **other care for screen-outs**, it is recommended that referral processes for those excluded from the trial should be specified in the protocol, implying that referral is an appropriate strategy here (cf. SA MRC, 2003). UNAIDS/WHO (2007) does not make recommendations for how these needs should be addressed even while alerting the reader that many conditions may be identified in screening, and UNAIDS/AVAC (2011) fails to mention volunteers in relation to non-HIV care. These recommendations suggest some agreement across ethical guidelines that obligations to screen-outs are not nil, and they deserve at the very least to be linked to services in the community that have been strengthened through capacity building steps by researchers (more on this point below).

The ethical guidelines agree that community members should benefit from trials through strengthened HIV services (SA MRC, 2003; UNAIDS/WHO, 2007; 2012). One ethical guideline also says that researchers must guarantee that communities have state of the art sexual and reproductive healthcare services (UNAIDS/WHO, 2007; 2012). These recommendations

suggest that guideline-developers agree that non-participants, in the form of community members, should access certain benefits from such trials (cf. Shapiro & Benatar, 2005).

#### 2.4.2.3 GUIDELINE RECOMMENDATIONS FOR ENGAGEMENT

Ethical guidelines also seem to agree on a series of engagement practices to ensure care for participants, volunteers and even participating communities. Ethical guidelines recommend *assessing health services*, more specifically that there should be a sound appreciation of existing health-care (SA MRC, 2003); that capacity to deliver HIV services should be explored (UNAIDS/WHO, 2007; 2012) and services for HIV and non-HIV care (and capacity) should be identified (UNAIDS/AVAC, 2011). Likewise, ethical guidelines agree on the need to *build capacity* of local systems (SA MRC, 2003; UNAIDS/WHO, 2007; 2012); more specifically to build capacity of trial-linked health care centres to deliver HIV services to the host community (SA MRC, 2003); and to strengthen local and national capacity to deliver the highest possible level of HIV services through strategic investment and development of trial-related resources (UNAIDS/WHO, 2007; 2012). Somewhat strangely, UNAIDS/AVAC (2011) no longer has a specific capacity building recommendation, unlike its predecessor (UNAIDS/AVAC, 2007).

Ethical guidelines agree on *assessing conditions* in the community, namely that researchers should have a good understanding of the health context of the community where the research will occur (SA MRC, 2003); and that vulnerability determinants should be analysed such as health conditions in participating communities (UNAIDS/WHO, 2007; 2012).

Ethical guidelines also agree that care is best implemented through partnerships between researchers and other key stakeholders. UNAIDS/WHO (2007) recommends that sponsor-investigators should *collaborate* with governments to strengthen HIV services to deliver the highest possible level of services, and that there should be *agreements* between partners regarding care (even while asserting that the local health-care system is primarily responsible for providing care services). UNAIDS/AVAC (2011) recommends that HIV care discussions clarify responsibilities between sponsor-investigators and health institutions regarding financing/ delivery of HIV services. SA MRC (2003) does not address partnership directly but

implies this approach in use of the term *trial-linked* centres. These recommendations reflect some consensus that – as treatment services become more scaled up in many countries– researchers should enter into strategic collaborations with service-providers to ensure needs are addressed (Macklin, 2008; Macklin 2010; MacQueen & May, 2008; MacQueen et al., 2008). These recommendations also imply that the most common response to needs will be referral or assisted referral to national programs, however one guideline states that there could be direct provision of selected services to HIV-infected participants until they are eligible for national programs (UNAIDS/WHO, 2007; 2012).

There are also several recommendations that implicate review by RECs. One ethical guideline asserts that care and treatment issues should be reviewed, more specifically, that reviewers should consider support, care and treatment to participants and to the community (UNAIDS/WHO, 2007; 2012). Another recommends that protocols should spell out expected benefits, which include access to HIV care (SA MRC, 2003) while another recommends that protocols should specify the procedures and interventions required for the research, and associated benefits, plus *other ancillary interventions, services and products*, and associated benefits. Listed benefits include: a care and treatment package for HIV infection, reproductive health care and contact with health-care workers (UNAIDS/WHO, 2007; 2012). UNAIDS/AVAC (2011) does not specify what should be in protocols with regard to care, only that teams/ stakeholders should discuss both HIV and non-HIV care during protocol development. These recommendations suggest some agreement that reviewers should have sight of the care steps that researchers plan to implement (cf. Participants, 2008) so that they can judge the adequacy of the proposed responses.

Ethical guidelines also make recommendations for consent materials and consent processes related to care. They assert that care for HIV infection should be in informed consent forms (UNAIDS/AVAC, 2011). They agree that participants must understand the care available to them if they get HIV infection (SA MRC, 2003; UNAIDS/WHO, 2007; 2012) and that stakeholders should discuss how to ensure awareness of HIV care-access (UNAIDS/AVAC, 2011). These recommendations suggest ethical guidelines agree that participants themselves should have a good understanding of care, even though the emphasis appears somewhat narrowly focussed on HIV care, and neglects to mention that participants should understand

fairly broadly how their needs will be addressed (cf. HPTN, 2009) especially as such issues are likely to be important to participants hoping to process the personal implications of trials (Lindegger & Richter, 2000; Lindegger et al., 2006).

Ethical guidelines all agree that stakeholders (including community representatives) should be involved in care decisions. More specifically, community representatives should *make inputs* into decisions regarding treatment and care linked to the research, such as helping researchers to work out how capacity should be built in local systems (SA MRC, 2003). Furthermore, research teams should *discuss* with relevant stakeholders HIV care (numbers, package, national guidelines and laws, mechanisms) and clarify responsibilities on financing and delivery of services (UNAIDS/AVAC, 2011). Research teams should *discuss* non-HIV care, both protocol-required services and additional services that community stakeholders would like to see offered to participants by the site (as well as strategies and impact). UNAIDS/AVAC (2011) asserts that negotiating the range of non-HIV related services will help ensure stakeholders understand available services. This reflects the understanding that there is an important role for community stakeholders in the care debate (MacQueen & May, 2008; Vallely et al, 2009) even while ethical guidelines emphasize slightly different practices (discussing, seeking inputs, negotiating). SA MRC (2003) and UNAIDS/WHO (2007) appear to recommend consultation about *HIV care*, whereas UNAIDS/AVAC (2011) recommends discussion about HIV care *and non-HIV care*, reflecting some awareness that the debate has moved beyond care for the endpoint (HIV) alone to encompass care for other conditions (cf. MacQueen et al., 2008; Participants, 2008).

UNAIDS/WHO (2007; 2012) states that there should be an on-going iterative consultative process to facilitate national decision-making about care and treatment (under a guidance point on benefits). It states that there should be a transparent, meaningful, participatory process that should involve all stakeholders before a trial starts to agree on the level, scope and duration of care and treatment (under a guidance point on treatment). It states that trials should not proceed unless all stakeholders have *reached consensus* on access to care and treatment (under the introduction). UNAIDS/AVAC (2011) does not have a consensus requirement, nor SA MRC (2003). Ethical guidelines recommend that approaches for access to HIV care be documented (UNAIDS/WHO, 2007; 2012) and that stakeholders discuss and

monitor these as well as document discussions (UNAIDS/AVAC, 2011). SA MRC (2003) does not address this issue. These recommendations reflect emerging awareness that stakeholders should be sufficiently engaged about care approaches to prevent misunderstandings and allegations of unethical conduct (Koen et al., 2012; McGrory, Irvin & Heise, 2009). These recommendations recognise that the multiple stakeholders who will be impacted by care-implementation need to be engaged early (Tarantola et al., 2007) and that evaluating the merits of various strategies can help strengthen such efforts (McGrory et al., 2009).

It is worth noting that SA MRC (2003) has the caveat that ethical standards should be enhanced by community consultation, whereas UNAIDS/WHO (2007) does not specify how the consultation process should be conducted in such a way that outcomes still meet other substantive requirements for care, for example that it be high quality (cf. London & Zollman, 2010).

Ethical guidelines present readers with several ethical rationales for taking steps to address medical needs in trials. Ethical guidelines refer to compensation for harm reasoning namely the possibility that participants might experience risk compensation from believing they are protected from HIV or that participants who are vaccinated and subsequently HIV-exposed may be more susceptible to HIV infection (SA MRC, 2003). Ethical guidelines refer also to beneficence-based reasons such as the need to actively promote the welfare of participants by addressing their HIV-related needs (SA MRC, 2003, UNAIDS/WHO, 2007) and to contribute to their welfare by ensuring access to non-HIV care (UNAIDS/ AVAC, 2011). Ethical guidelines also allude to justice-based reasons for ensuring access to HIV-care, namely, the need to reduce inequities in health-care between participants in sponsor and host countries (SA MRC, 2003) or to treat like cases alike by ensuring participants in high and low income countries are treated equally regarding access to HIV treatment and care (UNAIDS/WHO, 2007; 2012). The principle of justice as reciprocity is also briefly invoked by ethical guidelines as relevant to HIV care - insofar as UNAIDS/WHO (2007) asserts that participants should receive something in return for their time, inconvenience or discomfort.

From the review above, it is clear that ethical guidelines invoke a range of rationales for why care-related needs should be addressed. They make a series of recommendations about the steps that researchers should take in relation to participants' needs, and imply standards for researchers to strive for. They make recommendations about how various stakeholders should be engaged in care decision-making and implementation. Some have contended that the UNAIDS ethical considerations represent 'an ideal' (Macklin, 2010a, p. 202) and that 'strict adherence' may be hard to achieve in part because 'ancillary medical care is often not readily available' in resource-limited settings (Macklin, 2010a, p. 199).

### 2.4.3 SUMMARY OF ETHICAL GUIDELINES

In summary, ethical guidelines make many recommendations regarding care and treatment in HIV vaccine trials (also summarised in Appendix 1). Taken together, ethical guidelines recommend that researchers implement many responses to address participants' HIV needs and that participants acquiring HIV should have access to treatment that is 'high quality', from regimens internationally recognised as 'optimal' including ART, and treatment that is 'comprehensive'/ 'optimal' including ART. Ethical guidelines agree that HIV-infected participants should have access to a package of care for HIV, care for STIs, and for reproductive health needs. They agree that all participants (not just HIV-infected participants) should get treatment for STIs (through provisions on standard of prevention). All participants should get reproductive health care services (UNAIDS/WHO, 2007; 2012) and have supportive contact with health care workers (SA MRC, 2003, UNAIDS/WHO, 2007; 2012). This reflects increasing recognition that participants will present with a broader set of needs, including sexual/ reproductive healthcare needs. Ethical guidelines recommend that volunteers be referred to services (hopefully strengthened ones), reflecting recognition that obligations to such persons are not nil.

Ethical guidelines also recommend a series of practices to engage multiple stakeholders in care, reflecting recognition that many role-players will be impacted by (and can impact on) care. They recommend existing services be assessed, strengthened and partnered with. They imply that reviewers should be able to review protocols for care, by asserting that protocols spell out benefits including care. They recommend that participants understand HIV care.

They recommend that participating community representatives provide input into care decisions, discuss with researchers HIV care and negotiate with researchers about non-HIV care.

To date, there has not been detailed exploration of the concerns and complexities experienced by vaccine stakeholders in South Africa to establish if stakeholders are experiencing concerns or complexities for which ethical guidance offers helpful direction. I also raise this point after a review of prior empirical research, which follows in the next section of this chapter.

## 2.5 PRIOR EMPIRICAL EXPLORATIONS OF CARE

There has been longstanding debate regarding the role of empirical data in ethical debate (Holm, 2009; Hope, 1999). It is widely recognized that it is problematic to 'derive a moral conclusion *solely* from empirical findings' (De Vries & Gordjin, 2009, p. 199), that is, to deduce what should be done *solely* from a description of what is. Put another way, ethical norms should not merely mirror empirical findings (Kon, 2009) and empirical data cannot be the 'bottom line' (Goldenburg, 2005, p. 1). However many commentators have argued that empirical data may be significant for ethics (De Vries & Van Leeuwen, 2010). This so-called 'empirical turn' (De Vries & Van Leeuwen, 2010, p. 409) recognises that empirical data can 'yield information that is meaningful for ethics' in a number of ways (De Vries & Gordjin, 2009, p. 193). It recognises that empirical data does not in and of itself determine what should be, but can be relevant to such determinations (Barsdorf, Maman, Kass & Slack, 2010; Du Bois, 2009; Grady et al., 2008) and that refining normative recommendations can emerge from a process of reflecting on empirical data (Fry, 2009).

*Firstly*, data may illuminate stakeholder beliefs and views, not so that such intuitions can be uncritically accepted (Draper & Ives, 2007) but rather so that ethical recommendations can be framed in a manner likely to be perceived as relevant by stakeholders (Birnbacher, 1999 in de Vries & Gordjin, 2009). *Secondly*, data may indicate new ethical challenges or may find 'nuances in old problems' that require attention in normative recommendations (Draper &

ives, 2007, p. 322). Both of these may serve to help formulate ethical guidance in a way that is more contextualised or responsive (Carter, 2009). Thirdly, data may document gaps between espoused ideals and actual practices (Kon, 2009; Solomon, 2005 in Sugarman, Kass & Faden 2009) so that recommendations for practices can be made to bring them more in line with espoused ideals (Kon, 2009) or to promote reform in practices (Emerson, Upshur & Daar, 2009). *Fourthly*, data may also shed light on or counter prior claims or assertions that have been made in ethical debates (Emanuel, 2002a; Emanuel, 2002b). Sugarman et al. (2009) noted that caution must be exercised when recommending changes to policy or practice on the basis of a single study.

There have been several empirical investigations of care practices in HIV prevention trials, largely microbicide trials, as well in other types of studies. In this section these previous explorations are presented and possible implications for the ethical debate about care are considered.

One large study explored strategies to address care needs of participants at approximately twenty-four microbicide sites through discussions with site staff and CAB members, site visits and observation (MacQueen, McLoughlin, Alleman, McClain Burke & Mack, 2006; MacQueen & May, 2008; MacQueen et al., 2008). They found that most sites used a combination of direct care (on-site provision) and indirect care (referrals) to address participants' needs. Direct care was generally provided for acute more easily treated needs, such as STIs, although it was cautioned that costs of such an approach can accumulate across hundreds of participants (MacQueen et al., 2006). They found that sites implemented many measures to help participants access care through referrals, such as providing transport, generating funding to cover enrolment fees, providing medical documents to reduce referral-site burdens, reminding participants to access care, accompanying participants, asking participants for feedback, asking referral sites if participants presented for care, and contributing resources to partner organisations (time, training, supplies).

The authors found that there were several key factors affecting the balance of direct care versus referral (MacQueen et al., 2006). These included whether sites had in-house capacity to give direct care (trained staff, drugs); whether sites were located in a centre with care

facilities; the quality of care alternatives in the public sector (long lines, waiting lists, drug-stockouts, understaffing); the degree to which communities were empowered to negotiate with researchers to get benefits; and whether site-staff adopted a pro-active attitude to promoting participant well-being. They recommended several steps to engage key partners, including assessing care alternatives, developing referral systems, building relationships and establishing referral partnerships; and engaging the broader community to assess their priorities, attitudes and values (MacQueen & May, 2008; MacQueen et al., 2008).

They argued that, based on these engagement practices, researchers should determine whether care is to be provided directly, or via referral strategies. These authors asserted that care plans should be fair, and cautioned against meeting participants' needs in a way that creates 'health disparities through research' (MacQueen & May, 2008, p. 43). They cited the relative costliness of various strategies as a key consideration, asserting that responses should not deplete 'the time, resources and energy needed to do the research' (MacQueen et al., 2006, p. 8). They asserted that advantages of referral strategies include that participants' ongoing needs are served through keeping them connected to local care that will persist when trials close (MacQueen & May, 2008). This study did not explicitly aim to assess how well sites were implementing current ethical recommendations, nor to utilize data to inform a reflection on ethical norms. For example, even though this study found that communities were increasingly able to bargain with site-staff for benefits, it did not utilize this data to reflect on the moral negotiation approach (cf. Weijer & LeBlanc, 2006).

Heise et al. (2008) explored care at nine microbicide sites (including three sites in South Africa) through semi-structured interviews, document review as well as visits to sites and referral centres. This study aimed to explore care practices and decision-making about care to ascertain progress towards ethical aspirations, and to make recommendations to help the field address challenges. A component of the study was to explore how sponsor restrictions on care impacted on care practices (Philpott et al., 2010). The study found that care practices differed across sites in terms of what services were ensured, to whom and how. Heise et al. (2008) attributed such variation to various factors including investigator attitudes, co-location with care alternatives, partnerships with care providers and service-provider attitudes.

They found that sites took many steps to help participants who acquired HIV while on trials, including offering counselling, providing CD4 counts, undertaking prevention and treatment of opportunistic infections; and providing assisted referral to ART programs. Sites addressed STI needs by providing on-site treatment. Some sites addressed contraceptive needs by providing counselling but referring for provision, others provided counselling and provision on-site, and others referred for all contraceptive services. For participants who became pregnant while on studies, sites provided counselling and referrals for antenatal care.

Sites addressed participants' other, more general needs by referral, but at many sites participants were provided with on-site treatment (Heise et al., 2008). The authors reported that many researchers and site staff felt 'conflicted and uncertain' about their responsibilities to provide care for participants (p. 29) and reported the view that providing these services improved study outcomes through better retention, as well as 'benefitting' participants who were prevented from spending time and money seeking care elsewhere (p. 62). They found that protocols did not spell out steps for care of these more general conditions, or merely stated that 'non-study' care would not be provided. They found that site-staff went considerably 'beyond the care stipulated in protocols' (ibid, p. 29). It was argued that sponsor restrictions on funding care lead to such care being provided 'under the table' or 'not openly' (Philpott et al., 2010, p. 5).

The study found that site-staff took many steps to assist volunteers identified as HIV-infected at screening, such as offering counselling and referral to HIV programs and monitoring uptake of such services. They reported some challenges engaging screen-outs to take up care. They reported that some site-staff struggled over their obligations to screen-outs, especially when such persons had more advanced HIV disease than participants. In most instances, sites addressed STI needs with on-site treatment, and participants with pregnancies were referred for services.

Many site-staff felt 'conflicted' and unsure about their responsibilities to provide care for participating communities (p. 29) but few practices to strengthen care at local facilities to

improve care for community members were found. They found most sites had no mechanisms for engaging community in care-related decision-making; that most site-CABs were not consulted about care before protocols were approved, and only sometimes were asked to comment after protocols were approved.

The study found that many researchers felt called upon to provide ancillary care (not required to make the study scientifically valid, ensure safety or redress injury) (Philpott et al., 2010) and many sites implemented responses to help address participants' care needs even when this formed no part of the research protocol. It was argued that sponsors should develop policies that facilitate provision of ancillary care to participants (ibid).

This study noted some instances where practices did not appear to meet ethical recommendations (for example, they noted that while ethical guidelines call for community involvement in care-related decisions-making, local community involvement at sites was insufficient). A series of insightful recommendations were made to improve practices to bring them more in line with recommendations (for example, they recommended that community voices be integrated into care decision-making at all stages). There were few instances, however, where Heise et al (2008) utilized the practice data to reflect on ethical guidance. For example, they noted that most ethical guidelines do not address the issue of access to care for ex-participants, they identified this as a challenge identified empirically, they made practice recommendations (partnership, capacity-building, planning) but did not recommend that ethical guidelines be amended to include better direction on this point.

Clouse et al. (2010) assessed care for participants acquiring HIV during a HIV prevention trial of a diaphragm conducted in South African and Zimbabwe. They provided services to participants 'in-house' (such as counselling and provision of CD4 counts) as well as took many steps to ensure that participants took up services at referral points (PMTCT and ART) such as establishing agreements with referral points, booking appointments and tracking uptake. They prioritized linkage to care (or settling-in) within the public sector setting as a key researcher responsibility. Referral strategies were noted to present non-trivial costs to the research, including additional staff members employed for this purpose. They noted that only 6% of all their trial participants became HIV-infected, asserting that larger trials (or those

with more common outcomes) may need substantial additional resources to ensure ancillary services. They also reported implementing many responses for screen-outs with HIV, namely providing counselling, treatment for STIs, referral to local HIV care and detailed information on available studies.

They did not aim to compare their practices to ethical guidelines, but observed that their practices aligned with the UNAIDS/WHO (2007) guidance point on access to treatment, and aligned with the Four Ps (cf. Participants, 2008) insofar as they planned for sero-convertors needs, formed local partnerships with existing organisations, and took practical steps that included retaining staff post-closure to follow-up participants.

Ramjee et al. (2010) reported on care provision in large-scale HIV prevention trials in South Africa implemented by the Medical Research Council's HIV Prevention Unit. Researchers implemented various responses to help address participants' HIV needs, including providing CD<sub>4</sub> counts and viral load measures, and providing detailed referral letters. They reported some difficulties engaging participants for care, including denial and disclosure fears. They reported feeling tested about how far they should go to help participants with their needs, noting an example of a participant who acquired HIV, and TB, was subsequently paralysed and needed hospital and hospice care.

They implemented many responses to help participants with their sexual and reproductive needs, including counselling, and on-site provision of contraception. They responded to more general conditions (anemia, hypertension, diabetes) by referring participants to health-care partners in communities for care. They described a series of practices to engage service-providers including developing referral agreements, assessing available health resources, documenting such resources, and assisting with requests to build capacity at referral sites. They reported steps to address medical needs identified in volunteers, including providing contraceptive counselling. They also reported steps to benefit communities, such as providing STI education. These authors did not consider the implications of their practical experiences for current ethical recommendations.

Ngongo et al. (2012) explored care practices at ten sites conducting HIV prevention trials that were affiliated with the International AIDS Vaccine Initiative. They used a survey and interviews (or group discussions) with principal investigators, and other site-staff. They explored care practices for various groups (including participants, screen-outs and community members). They found that all sites took steps to assist volunteers and participants identified as HIV-infected, by providing counselling and referrals and many sites provided CD4 counts that enabled them to enter the care system with useful results. They provided volunteers and participants with management for STIs. Most sites addressed participants' family planning needs with counselling, and on-site provision of hormonal contraception, with some sites being able to provide other methods on-site; else referrals were made. Site strategies for addressing participants' other needs were diverse, with some assuming the service cost, and others making referrals to the public sector. They found reported challenges with referral strategies, including poor or inconsistent care at referral facilities, and limited feedback from such facilities. They also found that sites provided some services (such as STI services) to non-participants.

They reported their findings to principal investigators and site-staff to enable a process of developing more consistent standards across sites, or more standard approaches across sites. They made a series of recommendations for improved practices, for example, planning for care responses, good communication regarding the site's approach, and frequent review and revision of the site's approach. They expressed concern that when on-site services are provided to participants (and not other persons) this can be perceived as unfair or an undue inducement to enrol in trials.

Haire (2012) explored the views of fourteen principal investigators from twenty-eight HIV prevention efficacy trials regarding the clinician-researcher role, and associated conflicts, in semi-structured interviews. She reported that principal investigators recognized they had ancillary-care responsibilities and framed their ancillary-care responsibilities towards participants in terms of a 'doctor-like responsibility' (p. 5), and frequently invoked their clinician identity to justify 'participant-centered thinking' (p. 2). Principal investigators also reported that product-related increased susceptibility to HIV-acquisition in past microbicide trials impacted their sense of responsibility for ensuring participants access to ART. She

found that principal investigators saw their ancillary-care duties as balanced with other interests such as scientific integrity and budgetary constraints. She concluded that views of principal investigators were compatible with the perspective that researchers have ancillary-care responsibilities which are limited by certain considerations including the capacity of research sites.

Pratt et al. (2013) explored ancillary care practices of researchers at a malaria research unit in Thailand conducting a malaria treatment trial. Their methods comprised in-depth interviews with stakeholders, direct observation and document analysis. They researched whether ancillary care obligations were being met that were consistent with approaches to ancillary-care duties grounded in the reduction of global health disparities (cf. Benatar & Singer, 2000). More specifically that sponsors and researchers should improve the health of individuals in low-resource settings by providing care for a sub-set of conditions that cause severe mortality and morbidity to participants and their families without incurring costs that would usurp research (that itself is trying to achieve justice in global health).

They found that participants in the malaria treatment trial were treated for a wide variety of non-malarial conditions on-site as well as referred to various off-site providers, and in some instances the site paid fees for off-site treatment. Conditions for which care was provided included anemia, dengue, diarrhoea, STIs, typhoid fever, urinary tract infections and non-severe pneumonia. They found that treatment was provided on-site mainly for acute illness, and not chronic illness like diabetes or cancer, therefore noting that such treatment was provided for 'finite treatment period' and for a 'low treatment cost' (p. 9). They argued that researchers met and exceeded obligations on the model of interest. While they aimed to get data to inform the development of better guidance, they did not actually spell out the implications of their data for their favoured model, apart from noting that their data show that the model could be upheld in practice and therefore is feasible.

Taylor et al. (2011) explored ancillary care in public health intervention research through semi-structured interviews with public health researchers located in Asia that were conducting community-based studies and conducting facility-based studies. They found that researchers have two distinct ancillary care responses – namely where researchers make

decisions in advance of the conduct of their studies (*a prospective response*) and where researcher make decisions when they are in the field about whether ancillary care should be provided (*an ad hoc response*).

They reported that community-based researchers were more likely to adopt a prospective response than facility-based researchers. Community-based researchers reportedly provided many types of ancillary care to participants, such as health messages, education and counselling, malaria treatment, and treatment of STIs. Researchers justified such responses on grounds that they were simple, affordable, unlikely to compromise the study, and not routinely provided by the local health system. They also took steps to facilitate referrals, reporting efforts to survey available referral sources and to build capacity (either by training or giving supplies). The authors explicitly argued that their data may have implications for the ethical debate about ancillary care insofar as previous accounts have focused on the obligations of trained professionals to address ancillary-care needs, whereas their data showed that very often it is field staff in community-setting research that encounter ancillary-care needs of participants. They recommended that this issue should be considered in future normative discussions.

MacQueen et al. (2007) explored community stakeholder perspectives about the fairness of various strategies to address participants' HIV needs at ten sites conducting a microbicide trial in seven countries through interviews and focus group discussions with service-providers, community representatives, at-risk groups and participants. They hoped to include persons most directly affected by care decisions in the debate and conversation about care. They found that referrals to HIV care were perceived as a potentially fair way to address participants' HIV needs; but perceived fairness was linked to the effectiveness of such referrals, and commitment to addressing challenges at referral facilities. They found that community views about researcher obligations were framed as deriving from the relationship between researchers and participants but offered little detail. They recommended various ways to engage with partners at referral sites, more specifically that researchers identify existing resources for referral, evaluate capacity to absorb referrals, and hire staff to help participants to access care and monitor referral processes – in order to promote 'respectful, confidential and sustainable access to the best care possible' (p. 559).

Vallely et al (2009) assessed a community-engagement based approach to establishing an appropriate care package in a phase III microbicide trial in Tanzania. They engaged community representatives in a participatory process that included developing structures with representation from community and service-providers, and consulting them about services to be provided by researchers and hearing suggestions and recommendations for how participants' care could be improved (for example, streamlining services to reduce wait-times at clinics). They concluded that participatory methodologies enabled researchers and community stakeholders to dialogue and reach consensus on an appropriate care package in their setting.

Many proponents of ancillary-care responsibilities have called for additional empirical research into practices and perspectives. Participants (2008) noted that 'empirical research about researchers and research participants' attitudes, perceptions and expectations as well as about current ancillary care practices should be undertaken to inform the debate and development of appropriate guidance' (p. 7012/13). Dickert and Wendler (2009) noted that there needs to be more documentation about how ancillary-care needs are being met in particular settings. Hooper (2010) recommended more work be done to discover how researchers and other stakeholders 'actually deal with the problem of ancillary care' (p. 708). Richardson (2012c) noted there is much ignorance about researchers' ancillary-care practices, and about the attitudes of key stakeholders. He noted that as the debate progresses about standards of ancillary care to which researchers should adhere, it is imperative to learn more about what they are already doing. He noted that we also 'need to get a sense of whether they and others believe that they are not doing enough or, perhaps, are already doing more than they need' (Richardson, 2012c, p. 169). Pratt et al. (2013) recommended that approaches be described to generate more detailed guidance on how ancillary care obligations might be met.

### 2.5.1 SUMMARY OF EMPIRICAL EXPLORATIONS

In summary, there have been several empirical reviews of the practices of investigators, and their perspectives, regarding care in HIV prevention trials (Heise et al., 2008; MacQueen et al., 2008; Ramjee et al., 2010) as well as other kinds of research (Pratt et al., 2013; Taylor et al., 2011). These empirical studies have documented the care that is ensured for participants, volunteers and in some instances the broader community. These studies have also documented the care that is ensured for the endpoint of prevention trials, namely HIV, as well as for a broader range of health-care problems in these trials. To date, there has been only one such exploration for HIV vaccine trials (Ngongo et al., 2012). In addition, many of these studies assessed the degree to which practices meet ethical guidelines and when discrepancies were found, many helpful and insightful recommendations for *improving practices* were made to bring practices more in line with ethical recommendations (Heise et al., 2008). Other studies have assessed practices and where complexities have been reported by stakeholders these authors have made many useful recommendations for *improving practices* to address complexities (MacQueen et al., 2008). Few of these studies contained discussion of the implications for ethical guidance (cf. Du Bois, 2009) and in fact few of these studies have had the explicit aim of collecting data about practices and perspectives in order to make recommendations for *refining norms* and guidance about ancillary care, with a few exceptions (for example, Taylor et al., 2011).

### 2.6 SUMMARY OF THE LITERATURE REVIEW

In summary, there is still debate about the most appropriate grounding for sponsor-investigator ancillary-care responsibilities (Taylor et al., 2011) but no research exploring how vaccine stakeholders themselves understand or frame this responsibility. There is also still debate about the limits of researcher obligations to address participants and non-participants' needs (Taylor et al., 2011) and debate how best to engage the community, but to date there has been limited exploration of related experiences of key stakeholders involved in ancillary-care interactions at vaccine sites. Current ethical recommendations exist about ancillary care yet few studies have explored whether ethical recommendations address the concerns and complexities experienced by vaccine stakeholders. Prior empirical

explorations have been conducted yet few studies to date have explored whether ethical guidelines assist stakeholders with their contemporary problems in order to try to tailor guidance to the challenges and few studies have explored the implications of ancillary care experiences for refining ethical guidance (cf. Taylor et al., 2011).

In the light of these considerations, this study represents an effort to explore in detail the experiences of multiple stakeholders involved in South African HIV vaccine trials, with a view to not only documenting their conduct or practices but rather towards characterizing their contemporary concerns, challenges and complexities. Furthermore, this study is concerned not only with using data to improve practices, but rather also with using data to inform a critical reflection on ethical guidance. The following chapter describes the questions driving this study, as well as the methodology adopted.

# CHAPTER THREE

## STUDY AIMS AND METHODOLOGY

The chapter sets out the study aims, the broad approach to the study, the perspective in which this study is located, the methods adopted, and processes used to strengthen the rigor of the study including a reflexive account through-out. It also describes ethical parameters or efforts made to promote the rights and wellbeing of participants in this study.

### 3.1 STUDY AIMS

This study aimed to explore the experiences of key stakeholders regarding ancillary care in HIV vaccine trials in South Africa. The study aimed to explore not only the actions or conduct of critical stakeholder (the actual steps they take) but the meaning or significance they attach to their actions. More specifically, it aimed:

- i. To explore stakeholder practices and how stakeholders perceive, understand or make sense of ancillary-care practices in HIV vaccine trials
- ii. To explore stakeholders' contemporary concerns and complexities regarding ancillary care in HIV vaccine trials; and
- iii. To explore the implications of stakeholders' ancillary-care experiences for current ethical models and ethical guidelines.

## 3.2 STUDY APPROACH

### 3.2.1 A QUALITATIVE STUDY

This study adopted a qualitative approach. Durrheim (2006) noted that if the 'purpose is to study phenomena as they unfold in real-world situations, without manipulation' then a qualitative approach is appropriate (ibid, p. 47). Qualitative research allows researchers to study issues in 'depth, openness and detail' as researchers attempt to understand information that emerges from data, as opposed to beginning with pre-determined categories embodied in standardised measures (Durrheim, 2006, p. 47). It therefore seemed to be a sound approach for this study which aimed to explore and provide rich, detailed accounts of ancillary care. Snape and Spencer (2003) noted that qualitative research is a naturalistic approach concerned with 'understanding the meanings that people attach to phenomena' within their social worlds (p. 3). This seemed a sound approach for this study which aimed to provide an in-depth understanding of stakeholder's experiences and perspectives - held to be a central concern of qualitative research (cf. Snape & Spencer, 2003).

### 3.2.2 AN INTERPRETIVIST FRAMEWORK

Qualitative researchers are encouraged to outline their project's theoretical framework because the framework will impact how the issues are framed and the angle of investigation (Malterud, 2001). Snape and Spencer (2003) noted that qualitative researchers can hold diverse perspectives. This qualitative study is broadly located in an interpretive perspective, which focusses on actions, the subjective meanings that people attach to them, and the context (Fossey, Harvey, McDermott & Davidson, 2002; Ulin, Robinson, Tolley & McNeill, 2002). Identifying, sorting and analysing meanings in relation to actions and practices is asserted to be the substance of this perspective (Ulin et al., 2002). This perspective seeks to understand the meanings of actions and experiences, and views study participants as beings who engage in constant sense-making (Fossey et al., 2002). Silverman (2005) also noted a strong tradition in qualitative research which prioritises the study of perceptions and meaning.

Ulin et al. (2002) asserted that approaching problems from an interpretivist perspective means taking seriously individuals' subjective understandings, and linking these to their actions and potential impacts. Terre Blanche and Durrheim (2006) noted that the interpretivist perspective is most appropriate when the reality to be studied is people's experiences, when an effort is being made to explore and explain meanings behind actions, and the researcher cares about the meanings people attach to their experiences. This study was centrally concerned with a detailed exploration of stakeholder perspectives and actions in the context of HIV vaccine trials therefore this seemed to be a useful perspective within which to locate the research.

### 3.3 **STUDY METHODOLOGY**

This section describes the background to this study, the process by which interviewees were selected for this study, the process by which the semi-structured interview schedule was developed, how the ethical parameters were considered, how interviews were conducted and documents gathered, and the process followed to create codes and themes (steps 1 to 12). A reflexive account is incorporated which involves considering and disclosing 'the joys and mistakes' of the study (Tracy, 2010, p. 841). This section attempts to set out how the study has rigor and how the methods generated data that 'can provide for and substantiate meaningful and significant claims' (Tracy, 2010, p. 841). Read with the previous section, it is hoped that the reader will have sufficient information to judge whether the aims, theoretical framework, data collection methods and analysis are interconnected into a meaningfully coherent piece (cf. Durrheim, 2006; Quinn Patton, 2002a; Tracy, 2010).

#### 3.3.1 **BACKGROUND AND REFLEXIVITY**

At the time of conducting this study, I had been working for more than a decade (since 2000) as the Project Coordinator for a research and resource-development group focused on ethico-legal complexities in HIV vaccine trials, namely HAVEG based at the University of

KwaZulu-Natal (UKZN), South Africa. Our group was funded by SAAVI to conduct research into core complexities and implement capacity-building initiatives for stakeholders in HIV vaccine trials. I was originally trained as a clinical psychologist, and had conducted my Master's dissertation in ethical dilemmas of professional practice.

An early professional experience – with regard to the subject matter of this study - occurred in late 2002 where I was involved in hosting a HAVEG consultation (with key South African stakeholders) about various ethical complexities in HIV vaccine trials, including the issue of participants' access to ART should they get infected during a trial. At this consultation it became apparent that certain REC representatives and certain investigators did not have the same understanding of the precise approach to be adopted should participants acquire HIV and need ART (at that time not available in the South African public health system), and did not share the same understanding of what the REC had approved in this regard. This led the REC to suspend enrolment of trial participants in the current HIV vaccine trial pending agreement on the approach and a commitment to ART-access for participants (cf. Altenroxel, 2002). I felt quite responsible for creating the meeting space in which this confusion had been identified, while realizing I had little control over the particular response subsequently implemented.

Thereafter, I was involved in a national consultation in early 2003 convened by South Africa's Interim National Health Research Ethics Council to develop agreement about an interim measure to enable access to ART for HIV-infected participants, prior to roll-out of ART in the public health care system. As a result of these experiences, I assumed that stakeholders would likely have strong views about what was owed to participants with HIV (and possibly other health problems), that their viewpoints were unlikely to be identical, and that a complete consensus about the approach to be implemented in any one trial was likely difficult to achieve.

At around this time (2002), our group was also involved in adapting the international guidelines developed by UNAIDS for HIV vaccine trials (UNAIDS, 2000b) on behalf of the South African Medical Research Council that wished to add a booklet to their existing series of guidance booklets in South Africa (the others dealing for example with general

considerations, or animal ethics). One of the guidance points about which HAVEG received the most inputs from stakeholders was the guidance point addressing treatment access for HIV acquired during the conduct of these trials. We used outcomes from the consultations and inputs in South Africa (as well as existing norms) to inform the guidance that appears in that ethical guideline on the issue of treatment access for HIV infection (SA MRC, 2003).

From this series of professional experiences, I became very interested in the degree to which familiar ethical principles could be used to ground justifications for sponsor-investigators to ensure access to treatment. I partnered with a colleague with a background in philosophy (and other HAVEG members) to explore this issue, publishing a paper on it in early 2005 (Slack et al., 2005). The paper was subsequently rebutted (Schüklenk & Ashcroft, 2008) and countered (Stobie & Slack, 2008; Stobie & Slack, 2010). This set of writing experiences led me to believe that - while it was important to contribute to the normative debate – HAVEG did not have any empirical data on this issue and that empirical data might be helpful in strengthening approaches to this issue. At around this time, I was also a member of the African AIDS Vaccine Program's Ethics Law and Human Rights Working Group, where in 2004 I had been involved in an questionnaire-based review of ethical complexities reported by RECs in Africa (Milford, Wassenaar & Slack, 2006), including the issue of access to treatment, therefore I assumed that the issue posed a challenge to review bodies, but did not know exactly how the substantive details might manifest.

Over this period, I had also been involved in attending several training workshops and consultations where this issue was discussed including a workshop convened the National Institutes of Health Department of Clinical Bioethics on 2003 and a consultation convened by WHO/UNAIDS in 2003 (WHO/UNAIDS, 2004) as well as a consultation convened by the Global Campaign for Microbicides in 2004 (GCM, 2005) and one convened by WHO/UNAIDS in 2007, where I acted as rapporteur (WHO/UNAIDS, 2007). I was sensitized to many of the theoretical complexities at these consultations as well as interacted with some of the leading writers on the issue including but not limited to Henry Richardson, Ruth Macklin, and Kate MacQueen. At many of these consultations the recommendation was emerging that sponsor-investigators certainly had some responsibilities with regard to HIV needs, and that it was not acceptable to do nothing, but these experiences impressed on me that the justification being

favoured (the 'why') strongly influenced perspectives about what needs should be attended to, what parties should be attended to, and what steps should be implemented (the 'what' 'who' and 'how').

In 2009, as part of HAVEG, I was involved in securing a grant from the Wellcome Trust Biomedical Ethics Program to conduct an empirical exploration of ancillary care, as well as access to prevention modalities. The two-part nature of the exploration funded by the grant meant that I would be working closely with another researcher who was responsible for the exploration of prevention modalities, or so-called 'standard of prevention' activities related to HIV vaccine trials in South Africa. As a part of a review of studies (to secure the grant) I became aware that many conduct-type studies had been conducted to map the steps investigators were implementing to address medical needs in related studies, but that few studies had investigated in detail the viewpoints of stakeholders, and their perceived complexities but rather had tended to foreground practices, or actions or behaviours.

As part of the activities of the grant, I was involved in researching the reported conduct of key stakeholders in order to make comparisons with current ethical requirements (Slack, 2014). I was motivated to complement that exploration with an additional exploration that would illuminate in a more nuanced way the complexity of these stakeholder experiences. After the grant was awarded, I sought approval from the study sponsors to register for a PhD that would allow just this. This meant that my data collection, coding and analysis had a dual focus (to achieve the aims of the study grant as well as to achieve the ends of the PhD) and I had a 'dual role' (as a project researcher as well as a PhD student). In some instances, this dual focus impacted in a complicated way on my coding, as set out in the section on coding and analysis that follows later.

From my prior experiences, I was aware that people had different and varied views about the principles that best grounded care responsibilities, which impacted their understanding of who and what should be responded to. I was primed to search for accounts of why it was important to address such needs and expected to find such accounts and understandings, but I was not clear about the precise form these justifications would take. I was of the view that sponsor-investigators should take steps to address HIV needs (at the least to actively refer

people to reliable sources) and I expected to find these practice accounts for HIV, but I had fewer expectations about approaches for other needs. I also did not have a sense of the detailed micro-steps that could be implemented to help participants address their medical needs. I also anticipated that stakeholders would experience many challenges related to ancillary care, but was not sure of their precise manifestation.

### 3.3.2 PREPARING THE GROUND AND ADDRESSING ETHICAL COMPONENTS

After the grant was secured from the sponsor (the Wellcome Trust Biomedical Ethics Program) a stakeholder meeting was held prior to the implementation of any data collection. The consultation aimed to inform stakeholders that HAVEG wished to explore ancillary care and prevention practices (and related perspectives) and aimed to solicit their inputs. This was in line with ethical recommendations that relevant study stakeholders be engaged early (UNAIDS/AVAC, 2011).

It seemed important to have a good understanding of the possible implications and consequences for interviewees and the groups they represented considering that possibly sensitive information might be disclosed and placed in the public arena (Brinkman & Kvale, 2008). At this meeting, certain site-staff representatives expressed concern that less well established or resourced sites may be 'judged' by better established and more resourced sites, and experienced this as a potential research-related risk. Attendees were informed that these potential risks would be reduced to an acceptable minimum by various procedures (cf. Emanuel et al., 2000) such as anonymisation of individual respondents and sites, aggregation of site data into a national picture, as well as opt-out of questions.

In compliance with 571 of the National Health Act (SA Government, 2003) in South Africa, and national ethical guidelines (SA DOH, 2004), as well as ethical frameworks (Emanuel et al., 2000) the study was submitted for ethical review and approval at all RECs with jurisdiction over the HIV vaccine trial sites as well as at UKZN. These RECs were also notified of subsequent approvals from the Higher Degrees Committee regarding the subsequent PhD application. These RECs required certain amendments to be made to the consent forms (for

example to include contact details of the REC) and required that relevant gatekeeper permissions be obtained before accessing information at sites (cf. Wassenaar 2006; Wassenaar & Mamotte, 2012). The consent procedure for the study is described in a later section.

Early in the design of this study, care was taken to consider how individual interviewees would receive direct feedback about the study findings, and feedback was guaranteed in the consent form, and the protocol approved by the RECs. Care was also taken to consider how various stakeholders might be able to benefit from the study findings or how the results might be packaged and disseminated to various stakeholders at the end of the study. These steps were undertaken to meet ethical recommendations that study participants be provided with access to benefits in the form of knowledge generated (UNAIDS/ AVAC, 2011) and that the social value of the research be enhanced by providing feedback to various potential beneficiaries of the research (Emanuel et al., 2000). The implications for distinct stakeholder groups emanating from this study were carefully considered and are presented in the final chapter of this dissertation.

### 3.3.3 **DEVELOPING A SAMPLING STRATEGY FOR INTERVIEWEES**

In accordance with the aims of the study, purposive sampling was used which involves selecting participants who share particular characteristics and who can potentially provide rich, relevant, diverse information related to study questions (Tong, Sainsbury & Craig, 2007) or selecting a closely defined group for whom the study questions will be significant (Smith & Osborn, 2008). In some instances snowball sampling was used where interviewees were asked to identify suitable other interviewees who could help to develop insights about ancillary care in HIV vaccine trials (cf. Fossey et al., 2002; Kelly, 2006b).

Interviewees were selected from critical stakeholder groups, such as site-staff (including investigators), representative of the coordinating network, RECs and CABs because all these groups were involved in one way or another in addressing ancillary-care needs in trials, or reviewing plans to do so. It seemed likely that these stakeholder groups would be able to

shed light on the question of ancillary care and enable the development of a fuller understanding of the subject (cf. Brocki and Weardon, 2006). Interviewees were selected who had direct experience of the issue of ancillary care in HIV vaccine trials because they would be able to contribute their personal accounts and subjective experiences about ancillary care (cf. Smith & Osborn, 2008).

#### 3.3.4 ACCESSING INTERVIEWEES

It has been noted that participants who share a particular experience of a specific phenomenon can be difficult to access and careful engagement and rapport-building with core gatekeepers may be required (Smith, Flowers & Larkin, 2009). *Principal investigators and site-staff* were approached from all five preventive HIV vaccine sites in the country (including sites that had much experience with HIV vaccine trials and sites with less experience) that were implementing two particular HIV vaccine trials – a phase I trial and a phase IIB trial. More specifically, the phase I HIV vaccine trial explored safety and immune responses in vaccine recipients versus placebo recipients and enrolled participants at low-risk of acquiring HIV infection; whereas the phase IIB explored vaccine efficacy by assessing HIV infection, and viral load set-point, in vaccine recipients versus placebo recipients (in addition to evaluations of safety and immunogenicity) and enrolled participants at high-risk of acquiring HIV infection. These trials were selected because it seemed helpful to elicit accounts of experiences with ancillary care in actual trials rather than reflections about hypothetical or abstract trial scenarios. These two trials were selected because it was anticipated that their implementation would coincide with the period of data collection for the study. These two trials were also selected because they might possibly provide contrasting scenarios in which site-staff could reflect on ancillary care.

Representatives from all five *CABs* at the sites were approached. *Representatives from the network* were also approached. The network was responsible for securing funds from the sponsor, and for coordinating the conduct of HIV vaccine trials, and for taking on some responsibilities delegated to them from the sponsor such as development of informed consent forms. *REC members* at all four committees that had 'jurisdiction' over the relevant sites implementing HIV vaccine trials were also approached. A point-person at the United

States sponsor organisation that provided overall trial financing was also approached, however, email-efforts to liaise with the point person to secure a short-list of potentially interested persons to invite were not successful and after several emails the outreach was terminated.

The process for inviting potential interviewees was collaboratively designed, in order to minimize disruption to organizational processes and respect organisational procedures as far as possible (cf. UNAIDS/AVAC, 2011). In order to invite *site-staff* for interviews, a visit was arranged to describe the overall study, to identify concerns, to ascertain if there was broad interest, and to inquire about the best method to approach site-staff to take part in interviews. Concerns were tabled in visit reports and included concerns that interviewees may not be very familiar with ethical requirements, perhaps representing concerns that interviewees' ethical knowledge would be 'tested' in some way, and that interviewees should not be overly burdened by the time commitment required. There were questions about the possible impact of the research (representing occasional misunderstanding of this research as a form of an audit to establish compliance with ethical requirements). There were also questions about how to ensure that individual sites could get feedback if they so requested it without threatening the anonymity of particular interviewees, and discussion about how to ensure credible site-level data if only a few persons agreed to be interviewed per site.

A report was drafted for each site's principal investigator, describing the questions raised, how they were responded to and setting out the strategy proposed by attendees to invite potentially interested site-staff take part in the interviews (as well as CAB members, see below). The preferred strategy declared by site-staff was largely by email invitation. After approval by site principal investigators to proceed was received, email invitations were extended to site-staff to take part in interviews. Invited site-staff included principal investigators and site investigators, unit managers, study clinicians, and community liaison officers. In addition, letters were sent to site principal investigators, requesting access to documents for the two selected HIV vaccine trials – including protocols, ethics applications, informed consent forms, and other relevant documents (see Appendix 2).

For *CAB* members, presentations were made to CAB members at all five HIV vaccine trial sites; their questions addressed (see below) and their preferred strategy to be invited was identified, which was largely via cell phone. Most CABs elected not to send the full list of cell phone contacts but rather sent a 'short-list' of representatives willing to be contacted, after discussing amongst themselves the nature of the research, and the suitability and interest of individual members.

For *network representatives*, an email was sent to the representative of the organization, requesting the opportunity to approach interested potential interviewees. After this request, a list of names of persons willing to be contacted was received. Those persons were sent an email inviting them to take part in interviews. The network was also requested to release master protocols for two HIV vaccine trials being conducted in South Africa at that time, which they did.

For *RECs*, an email was sent to the Chair of all four RECs that had reviewed HIV vaccine trial protocols in South Africa. The email requested access to the contact list of members, and made assurances that the list would not be circulated and would only be used for study purposes. In most cases, the Chair provided access to the entire list of members, however, in one case, the Chair provided access to a shorter list of members who had agreed to be approached. Members were sent an email inviting them to take part in interviews.

This strategy for identifying (collaboratively) with potential participants the most appropriate manner to approach people to be invited must have some impact on the interview data. One could speculate that the 'short-list' approach adopted by most CAB approached for the study, and by one REC, might mean that some self-presentational work was being done whereby persons considered best able to represent the views of the group were asked to consider participating; or more benignly it might mean that only persons sufficiently interested or motivated allowed themselves to be named for a subsequent approach.

### 3.3.5 DESIGNING SEMI-STRUCTURED INTERVIEW SCHEDULE

A semi-structured interview schedule was designed to elicit accounts of practices and perspectives regarding various health needs and related issues (described more fully below). The interview was understood as an interaction co-produced by the researcher and interviewee, whereby both parties would influence the agenda (Reynolds & Prior, 2003). The semi-structured interview schedule was viewed as a guide that would not dictate the precise course of the interview (Dunn & Quayle, 2001) but would allow an exploration of key components of ancillary care fairly systematically. Questions were open-ended where interviewees were encouraged to talk about their practices and experiences, and interviewees could express themselves in their own terms and offer their own definitions (cf. Giacomini & Cook, 2000). The interview schedule made use of funneling where general views were elicited first then respondents were funneled into more specific questions through the use of explicit prompts (Quinn Patton, 2002b) and it was flexible enough to allow some complexity to be unraveled (Smith & Osborn, 2008). It was necessary to obtain an account of actual conduct which required the use of specific prompts to elicit such practice accounts (for example, *'so can you clarify if referrals are made or if participants are treated onsite?'*). These prompts seemed sometimes to interrupt a more free-flowing account of their experiences about care which was countered by re-inviting interviewees to reflect broadly on their experiences.

For *site-staff (and network representatives)* the interview schedule covered the following domains:

(\*) their role in HIV vaccine trials and involvement in care issues

(\*) their view of the most important issues regarding care and treatment in HIV vaccine trials generally

(\*) their view of the key issues regarding addressing needs in volunteers, as well as views on complexities about care for volunteers, as well as the practices implemented (at the site) for volunteers with care needs

(\*) their view of the most important issues regarding care for participants with HIV

- (\*) the actual practices implemented (at the site) to address participants' HIV needs and associated complexities
- (\*) their opinion of the reason that participants' HIV needs should be addressed
- (\*) their views of select ethical guidance
- (\*) their view of the most important issues regarding sexual and reproductive healthcare for participants
- (\*) the practices implemented at the site to address participants' sexual and reproductive healthcare needs (contraception, pregnancy, STIs) and any associated complexities
- (\*) their viewpoint about why it is important to address sexual and reproductive healthcare needs
- (\*) the steps or practices implemented (at the site) for other, more general healthcare problems identified in participants, and associated complexities
- (\*) their view of the reasons why such general needs should be addressed
- (\*) their experience of establishing relationships with key role-players such as service-providers at referral centres, representatives from the network, RECs and participating community regarding care
- (\*) the practices implemented at the site to engage participating community and CAB representatives about care, and views about related complexities
- (\*) the practices regarding provision of services to non-participants (community members) or investing in care facilities serving non-participants
- (\*) the practices regarding spelling out care steps in protocols and consent materials and views about such materials development
- (\*) their views on any care-related issue they deemed to be significant that the schedule had not covered.

For *CAB members*, an adapted schedule was developed to elicit their perspectives and practices regarding care in HIV vaccine trials because it was anticipated their practices would

logically differ from site-staff and network representatives. This schedule covered the following domains:

- (\* ) their role on the CAB
- (\* ) their personal view of the most important issues regarding care and treatment in such trials
- (\* ) their understanding of the care issues that are of concern to the CAB
- (\* ) their understanding of the reason that participants' needs should be addressed
- (\* ) the role and function of the CAB, including the practices of the CAB regarding the review of protocols and materials for such trials
- (\* ) their understanding of researcher practices for care in such trials
- (\* ) the experiences of researcher engagement practices at the site or their experiences of being engaged by researchers for care
- (\* ) their views of select ethical guidance
- (\* ) their views on any care-related issue they deemed to be significant that the schedule had not covered.

For *REC representatives*, a slightly adapted schedule was developed because it was anticipated that their practices would also differ from those of site-staff or network representatives (for example, it would make no sense to ask REC members what steps they took to personally help address needs because their practices would centrally relate to review of protocols for HIV vaccine trials). Other components of the schedule remained similar in order to allow comparison across stakeholder groups (for example, questions eliciting their personal views about why participants' needs should be addressed).

The schedule covered the following domains:

- (\* ) their role on the REC and involvement in the review of HIV vaccine trials

- (\*) their view of the most important issues regarding care and treatment in such trials generally
- (\*) their practices regarding the review of protocols for such trials and any associated complexities, including the care issues the REC looks for when implementing such reviews and associated complexities
- (\*) their personal views about the key issues regarding HIV care, sexual and reproductive health-care and general care for participants
- (\*) their understanding of the expectations or requirements from the REC regarding researcher practices for care in such trials
- (\*) their personal opinion of the reason that participants' needs should be addressed
- (\*) their views of select ethical guidance
- (\*) their experience of interacting with researchers
- (\*) their views regarding the protocols and consent forms submitted by researchers
- (\*) their views on any care-related issue they deemed to be significant that the schedule had not covered.

The schedule aimed to elicit actions and perceptions (Ulin et al., 2002, p. 44). The schedule was refined as data collection proceeded, for example, after conducting three interviews, it was apparent that some interview questions were being perceived as too vague, therefore efforts were made to make perspective questions more precise and brief prefatory statements were added (cf. Quinn Patton, 2002b). For example, before the question "*what do you think is the reason that participants' needs should be addressed?*" the statement was added "*This is deliberately broad question but your personal view is very important*". Transcription was undertaken that would allow all the spoken words to be viewed, including errors (Fossey et al., 2002).

### 3.3.6 ENSURING INFORMED CONSENT

Prior to the commencement of every interview, participants were asked to send a signed consent form (see Appendix 3). In addition, before the interview participants were reminded that the study aimed to understand stakeholder perspectives and practices regarding care in HIV vaccine trials, that their individual responses would be anonymised and integrated into a general overview, that if there were any issues they did not want to discuss they were free to decline to answer, that the purpose of the interview was to get their insights about care in HIV vaccine trials, and invite them to ask questions, as well as inquire if they were happy to proceed.

It was considered very important to take trouble with the consent process for this study. The functions of informed consent include to ensure that participants enroll in studies when such enrolment is consistent with their values and preferences (Emanuel et al., 2000) and with a sound understanding of potential risks and benefits attached to key study components (Weijer, 2000) and the personal implications (Lindegger & Richter, 2000). Some aspects of a study might be considered especially important for participants to understand – so called deal-breakers – because the consequences of misunderstanding them are potentially severe (cf. Lindegger et al., 2006). Potential participants need to understand possible risks and how these will be minimized. Some care was taken to consider potential risks in advance and outline them simply in the consent form. The consent form outlined this issue in some detail – stating:

*If you are taking part in an interview, you may feel worried to talk about care (...) practices that are not working well in the group or institution that you are a part of. You may worry that talking about these will have negative consequences for you or your organisation. Remember that you can choose not to take part, or not to answer certain questions. You can also make your answers general and not about your actual organisation. We will make every effort to make your responses anonymous. We will not report any names of people when writing reports. We will group together information about sites into a national 'picture' before any public release. This information will be shared with stakeholders at a national consultation before public*

*dissemination. We are not tasked to monitor practices. However, if you inform us of something that appears to be a serious breach of practice that poses a direct risk to the health and welfare of an actual HIV vaccine trial participant, then it seems wrong for us to do nothing. So in this event, we will discuss the issue in a confidential research meeting. We may ask you for more details. A decision may be made to contact the site Principal investigator for clarification and remedial action if necessary. In this event you will be informed and every effort will be made to maintain your confidentiality and resolve the issue in a collegial and respectful manner. Sites may have to contact their REC and/or other institutional bodies as per their own arrangements.*

While the consent form was seen as an important component, the introductory remarks were also important because one of the best ways to promote understanding of participation is by spending time discussing the issues with potential participants (Flory & Emanuel, 2004). It also seemed hypocritical to conduct a so-called ethics study that did not in and of itself collect data in a manner that respected participants' welfare and rights.

### 3.3.7 CONDUCTING INTERVIEWS

Face-to-face interviews were conducted with two participants, and the remaining interviews were conducted over the telephone. Permission to tape record was granted by almost all participants, with only one declining to be recorded. Interviews took place between September 2010 and September 2012.

For *site-staff*, I personally conducted eleven interviews (at least two per site). Six of these interviewees had had previous personal contact with me – including attending SAAVI meetings and hearing presentations on project work at such meetings. Prior interactions also included incidental meetings during my visits to sites on other HAVEG-related activities, and contact related to accessing sites to implement such activities. In addition, a colleague interviewed six of the same participants as I did - for prevention modalities - where-upon a few care-related references were made and therefore extracted. This same colleague also

interviewed six new site-staff about prevention modalities where-upon a few care-related references were extracted however these did not form part of my primary analysis because they added little to the exploration of subjective experiences of ancillary care. Therefore the data set for the analysis of site-staff interviews comprised eleven participants.

For *network representatives*, I personally conducted three interviews. I had experienced prior contact with one interviewee related to a previous project. In addition, a colleague interviewed one of the same interviewees and where this same interviewee made care-related statements, these were extracted. Furthermore, one new representative was interviewed about prevention activities and this text did not form part of this analysis. Therefore the data set for the analysis of network interviews comprised three participants.

For *CAB* representatives, I personally conducted one interview and had no pre-study contact with that interviewee. A colleague conducted interviews about both care and prevention with an additional six representatives. Care-related text from those interviews was coded. None of the six participants were known to me. Of those latter interviews, two were considered unsuitable for a detailed nuanced exploration of experiences, and were not included in my analysis. Therefore the data set for the analysis of CAB interviews comprised five participants.

For *REC* representatives, I personally conducted six interviews. I had prior contact with three interviewees, related to national meetings and conferences around unrelated ethical topics. In addition, a colleague conducted interviews with two additional representatives about both care and prevention and where care-related references were made these were extracted and did form part of the analysis. Therefore the data set for the analysis of RECs interviews comprised eight participants.

In total, the data set for the analysis of interviews comprised twenty-seven participants. I had, therefore, been engaged in other forms of pre-study interaction with many (but not all) of my interviewees (eleven out of all the interviews I conducted). It has been argued that the researcher must consider what kind of information is likely to be shielded from the researcher

versus made more readily available (Tracy, 2010). It seems possible that these prior contacts – as the HAVEG project coordinator - meant some investigators/ site-staff had concerns that I was looking for accounts of practice falling below ethical-guideline recommendations and were motivated to put their best foot forward by presenting sanitized or socially desirable accounts. It also seems possible that some REC representatives might also have been motivated to frame their practices as especially rigorous – thereby doing some ‘presentational work’ to convey their replies in a manner thought socially desirable or using so-called ‘self-presentational devices’ (Brocki & Weardon , 2006, p. 90).

However, a core message as part of study outreach was that the study sought stakeholder views, perspectives, and insights about ancillary care, and that a lack of correspondence with guidelines would not be uncritically read in favour of guidelines, more specifically, that a critical reflection on ethical norms was as important as a critical reflection on practices. In general, HAVEG has attempted to be even-handed in the development of resources that might serve RECs *and* investigators, and it was hoped that this stance would precede the actual data collection for this specific study. Additionally, many stakeholders presented accounts of questioning their own practices (see the results chapter) that suggested not only ‘socially desirable’ responses were being reported, but also critical self-reflection about practices, which was somewhat reassuring.

The group for which I am the project coordinator is committed to HIV vaccine trials (albeit trials that are in a particular ethical ‘shape’) and has been part of a larger initiative committed to the same overall effort, and I had prior contact with several interviewees in this study. Therefore I recognised the important challenge of balancing of an empathic reading of participants’ accounts with a more critical interpretation of what such accounts might mean in the theoretical arena of ancillary care (cf. Kelly, 2006a).

### 3.3.8 SAMPLE CHARACTERISTICS

Study participants were drawn from site-staff at all five preventive HIV vaccine sites in the country that were implementing two particular HIV vaccine trials – a phase I trial and a phase

IIB trial. They were also drawn from all CABs at sites, and from the network responsible for securing funds from the trial sponsor and for coordinating the implementation of the trials. Study participants were also drawn from REC members at all four committees that had ‘jurisdiction’ over all the sites implementing HIV vaccine trials. See the table below.

Table 1: Summary of study participant numbers per stakeholder group

Site staff	11
Network	3
CABs	5
RECs	8

In terms of *site-staff*: Site-staff representatives undertook various roles and responsibilities at HIV vaccine sites, and therefore were likely to contribute various perspectives regarding ancillary care. They comprised principal investigators in charge of overall execution of specific protocols at the site who were often simultaneously the site leader responsible for the centre’s overall activities. They also comprised persons responsible for co-ordination of specific trials including the implementation of protocols in compliance with ethical and regulatory approvals, and the development and implementation of standard procedures for implementing protocols. They also comprised persons responsible for clinical management of participants’ medical conditions. Lastly, they comprised persons responsible for liaising with community representatives and undertaking preparedness activities (and other engagement functions) with participating community representatives. It was critical to secure interviews with persons in leadership roles for both protocols, and for all sites, in order to explore first-hand experiences directly related to the study questions, including detailed accounts of practices.

In terms of *network representatives*: Study participants undertook various responsibilities including management and implementation of trials, including appropriate ethical standards. More detail on actual functions and titles would likely lead to the inadvertent identification of these participants, at least to those with sufficient insider knowledge – referred to by some as deductive disclosure (Tracy, 2010).

In terms of *CAB representatives*: Study participants comprised both fairly senior members with considerable experience including participating in site and network processes, as well as members who were less experienced with regard to HIV vaccine trials.

In terms of *REC representatives*: Study participants also were involved in a variety of roles and functions, including acting as overall Chairpersons with functions that included assigning reviewers, and managing meetings. They comprised members of the committees who had reviewed HIV vaccine trial protocols and participated in discussions about such protocols at meetings and had diverse expertise including infectious diseases, epidemiology, social sciences and bioethics.

### 3.3.9 CODING AND ANALYSIS

Malterud (2001) recommends that researchers 'follow a path that has been trodden by others' (p. 487). To structure an approach to coding and analysis, guidelines for Thematic Analysis (Braun & Clarke, 2006) were used, which were supplemented with guidelines for Interpretative Phenomenological Analysis or IPA (Smith & Osborn, 2008; Willig, 2008). It was hoped that by supplementing guidelines for Thematic Analysis with recommendations from IPA, themes could be developed that captured meanings attributed by participants to their experiences (Willig, 2013). The latter has been argued to be a useful analytic approach when issues related to 'sense-making' are important (Smith & Osborn, 2007, p.520) and when the issues are 'complex' or 'dilemmatic' (Smith, 2002, p. 132/3 in Brocki & Weardon, 2006, p. 99) or of 'considerable moment' to participants (Smith, 2004, p. 49).

IPA is centrally concerned with subjective experience (Eatough & Smith, 2006) specifically the texture of experience (Willig, 2008). Besides often being used to explore topics in health (Brocki & Weardon, 2006) it seemed to be a most appropriate analytic approach for this study because it aims to establish 'how participants are *making sense* of their personal and social world, and the main currency for such a study is the *meanings* particular experiences (...) hold for participants' (Smith & Osborn, 2008, p. 53) or the meanings that are assigned to experiences (Brocki & Weardon, 2006; Osborn & Smith, 1998). It is concerned with how

individuals perceive the particular situations they are facing, how they interpret their experiences (Reynolds & Prior, 2003), and their personal accounts of a phenomenon (Smith & Osborn, 2008).

IPA assumes that participants' experiences are mediated by the expectations they bring to bear (Willig, 2008). Participants are understood to be self-interpreting (Koch & Harrington, 1998) and meaning-making agents (Eatough & Smith, 2006). It assumes that it is impossible to gain direct access to participants' worlds and that researcher conceptions are a 'necessary precondition' for understanding such experiences (Willig, 2008, p. 69). Therefore the knowledge produced using this approach is reflexive (dependent on the researcher's standpoint) and not naively realist. The resultant analysis necessarily implicates the researcher's view of the world. The analysis is held to involve a double interpretation process where the researcher attempts to *make sense* of the participants trying to make sense of their experiences (Smith, 2004; Smith & Osborn, 2008) and where the researcher is involved in a process of 'interpretive engagement with the texts and transcripts' (Smith, 1997, p. 189 in Willig, 2008, p. 57). Analysis is therefore committed to foregrounding participants' subjective experiences while recognizing that this requires interpretive work from the researcher (Smith & Osborn, 2007).

The active role of the researcher in developing themes and reporting them is acknowledged (Taylor & Usher, 2001 in Braun & Clarke, 2006, p. 80). The approach may refer to themes that 'emerge' from the data, however, this is viewed as a selection process requiring interpretation on behalf of the researcher (Flowers, Duncan & Frankis, 2000). It is understood that the analytic account rests on the joint reflections of participants and the researcher (Brocki & Weardon, 2006). The researcher seeks to understand the account presented by participants whilst simultaneously making use of his or her 'interpretive resources' (Smith, 1999, p. 223 in Brocki & Weardon, 2006, p. 96). It is understood that participants' meanings are not merely available but must be 'obtained' through a process of interpretation (Smith & Osborn, 2008, p. 65). This approach views both the participant and the researcher as participating in the process of sense-making (Smith, 1999).

The researcher should foreground the study participants' perspective as well as offer an account of what it means for study participants to have these concerns in their context (Larkin, Watts & Clifton, 2006). This can exceed the terms and conceptualizations used by participants (Smith, 2004, in Larkin et al., 2006). The researcher is free to draw on various interpretive possibilities provided that a recognizable core account focussing on participants' experiences is visible and central (Larkin et al., 2006; Reid, Flowers & Larkin, 2005). The researcher should combine an *empathic* stance, where the researcher is trying to understand participants' viewpoints and experiences, with a more tentative *questioning* or interpretive stance where the researcher tries to gain insight into the nature and meaning of those experiences (Willig, 2008). It is recommended that the empathic reading be done first, followed by a more critical yet speculative reflection (Smith, 2004). This approach does not attempt to bracket previous knowledge to better understand the essence of a phenomenon as advocated by some traditions of phenomenology (Willig, 2008). However, the researcher should foreground the participants' accounts *before* making theoretical connections, or drawing on theoretical accounts, or locating experiences in the existing literature (Eatough & Smith, 2006; Green, Willis, Hughes, Small, Welch, Gibbs & Daly, 2007; Larkin, Watts & Clifton, 2006). The overall outcome should be renewed insight into the phenomenon as experienced by participants (Larkin, Watts & Clifton, 2006) where the reader's appreciation of subject matter is clarified and expanded (Elliot, Fischer & Rennie, 1999).

The steps recommended by proponents of Thematic Analysis (Braun & Clarke, 2006) and IPA (Smith & Osborne, 2008; Willig, 2008) were summarized, and a 'hybrid' set of steps was developed. There was overlap between them, but these authors appeared to use different terminology for labelling a basic segment of text with Braun & Clarke (2006) referring to 'codes' and Smith & Osborn (2008) referring to 'themes'. The following steps were undertaken:

#### 3.3.9.1 *Step 1: Reading and re-reading the interview transcripts*

In this preliminary step, the researcher is encouraged to read and re-read the text (Braun & Clarke, 2006; Willig, 2008). In these initial readings the party being referred to was noted - enrolled *participants* or persons that *volunteered* to take part but did not necessarily get enrolled or to *community members* more generally. In these initial readings the need being

referred to was also noted - HIV needs or sexual/ reproductive needs or more general conditions. These references in the transcripts were not at all surprising because interviewees had been asked questions about these parties and needs during semi-structured interviews.

### 3.3.9.2 *Step 2: Developing first-level codes*

In this next step, the researcher is encouraged to code the text by assigning labels to basic segments of the text (Braun & Clarke, 2006) or attributing a word or phrase to segments of text (Green et al., 2007). The text was assigned a code according to the practices being referred to - using verbs or the language of practices, such as '*providing HIV counselling to participants onsite*', or '*counselling participants to access HIV care*'. It was important to identify actions that were being implemented by site-staff, and other stakeholders, as part of the process of identifying how they make sense of their actions. Codes were 'active' and 'specific' to help identify practices that may otherwise remain implicit (Charmaz, 2008, p. 98). Codes took the form of meaningful phrases (Miles & Huberman, 1994).

I was previously sensitised to certain practices recommended in ethical guidelines, and found in previous empirical assessments, such as '*referring for ART*'. These constituted deductive codes or 'top-down' codes (Quinn-Patton, 2002a). However many practice codes were developed from reading of transcripts, such as '*seeking permission to share results*' that constituted inductive or 'bottom up' codes. Therefore a combination of deductive and inductive coding was used. In assigning these practice codes, text was labelled in a semantic and explicit way, using the surface meanings of the data (Braun & Clarke, 2006) or 'everyday terms' (Sandelowski, 2000, p. 338). It was hoped that these codes would be accessible and credible to the persons who provided the information and relevant stakeholders (Quinn Patton, 2002a). Text was also labelled to capture key perceptions, that is, how interviewees were seeing things or how they were understanding things or how they were making sense of their actions. In assigning labels here, efforts were made to stay close to the words used by interviewees to ensure their viewpoint was being foregrounded. Examples of sense-making codes include ones such as '*seeing as a response to participants' contributions*' or '*seeing that participants 'step up*'. Adopting this kind of coding was a deviation from recommendations in IPA that assigning labels at this early stage be conceptual using theoretical terminology at a higher level of abstraction (Smith & Osborn, 2008; Willig, 2008).

### 3.3.9.3 *Step 3: Listing first-level codes*

At this stage, the researcher is encouraged to list their emerging codes for each separate interview and examine them closely (Willig, 2008). Problems were identified at this early stage. A review of the codes generated for the first few interviews showed far more 'action' (practice) codes than 'sense-making' or perception codes. It seemed that the need to document actions or practices articulated by interviewees was interfering with coding text capturing how they were making sense of their experiences. This 'practice-focus' was linked to my involvement in the broader project (funded by the Wellcome Trust) that aimed to assess whether stakeholder practices for care (and prevention) corresponded with ethical requirements. That project aim required that practices be articulated and evaluated to see how well they resonated with expectations set out in ethical guidelines. Ethical guidelines appear primarily concerned with stakeholders' conduct (and less with their perceptions) therefore to implement that funded project properly a clear account of conduct was required. To ensure a clearer account of how stakeholders were making sense of their actions, initial interviews were re-coded.

### 3.3.9.4 *Step 4: Sorting first-level codes into code-clusters (sub-themes)*

At this stage of the process, the researcher is encouraged to think about the codes in relation to one another, to cluster codes that can be logically combined, or that share meanings or references (Boeije, 2002) or to look for connections between them (Willig, 2008) – here the researcher is asked to imagine a magnet pulling some codes together (Smith & Osborn, 2008). More broadly qualitative researchers are generally encouraged to organise codes into groups at a different level of abstraction (Elliot et al., 1999) or to consider how codes that share a relationship can be linked to create coherent categories (Green et al., 2007). Miles and Huberman (1994) liken this to a statistical factor that groups material into a more coherent whole. In other instances, the researcher is asked to consider whether the relations between codes are hierarchical and whether such codes should be ranked (Willig, 2008). The researcher is encouraged to assign names to these code-clusters that capture their essence, and these code-clusters are considered sub-ordinate themes (Willig, 2008) – hereafter referred to as sub-themes.

For practice codes, this task was relatively straightforward. For example, the following codes were clustered: *'providing participants with counselling for HIV onsite'*, *'referring for ART'*, *'encouraging participants to take up HIV care'*, *'drafting comprehensive HIV treatment plan for participants'* and *'establishing HIV treatment fund for participants'* and assigned the code-cluster name of *'Taking steps to help address participants' HIV needs'*. The same relatively straightforward identification and clustering of practice codes was undertaken for STIs and other needs (contraceptive needs, pregnancy needs, and general conditions) for both participants and volunteers. For the sense-making or perceptions codes, this task was more complex, but began with the creation of codes such as *'responding to risk assumption'* and *'responding to effort'* which began to capture respondents experiences that, by taking steps to help, they were reciprocating for valued contributions. These code-clusters constituted preliminary subordinate themes (Willig, 2008).

It was been noted that a theme represents 'some level of patterned response or meaning within the data set' that captures some significant aspect of the data in relation to the study question (Braun & Clarke, 2006, p. 82). Others have described a theme as 'a recognizable configuration of meanings which co-occur in a way that is meaningful and systematic rather than random and arbitrary' (Willig, 2013, p. 59). Efforts were made - at this early stage - to ensure that code-clusters were a coherent constellation of sense-making first-level codes.

The first series of interviews were all with site-staff, who were working at two of the five sites conducting trials across the country. Practices about how sites were implementing strategies to address the medical needs they identified were compared and contrasted. This task would continue for the remainder of the interviews with site-staff until a cross-site account was generated of site-staff practices for HIV care, sexual and reproductive health care and general care (cf. Quinn Patton, 2002a).

#### 3.3.9.5 *Step 5: Developing theme tables for individual interviews*

It is recommended that qualitative researchers use visual aids to help them to organise their codes into sub-themes (Braun & Clarke, 2006) - that is, researchers are encouraged to use aids to help them conceptualise patterns in the data and the relationships between them

(Braun & Clarke, 2006). In IPA, it seems a particular kind of visual representation is recommended, namely a table and it is recommended that *after each interview* the researcher develop a table that visually displays 'codes' structured into sub-themes (Willig, 2008). Therefore, for each interview, a table was developed that included extracts labelled with particular tags (codes) clustered into code-clusters. The tables also showed anonymised participant identifiers, as recommended (Willig, 2008). These tables reflected first-level codes clustered where they shared meanings (Willig, 2008).

#### 3.3.9.6 *Step 6: Developing themes tables across interviews*

After about every three interviews, individual theme tables were studied for shared experiences and a master theme table was developed that represented first-level codes clustered into code-clusters (sub-themes) for all the interviews. Sub-themes were also clustered to develop over-arching themes (Braun & Clarke, 2006) or master themes that tried to capture shared experiences of the phenomena under investigation (Willig, 2008). For example, one such master theme table (originally named '*Seeing differences*' in care but eventually named '*Privileging*') visually represented various code-clusters (sub-themes) from multiple interviews concerned with differences in care between participants and citizens as well as between participants at different sites and related tensions and ambivalences.

#### 3.3.9.7 *Step 7: Coding documents*

At this time, many relevant documents had been obtained as a result of the engagement process outlined earlier. These included master protocols (forwarded from the network) and actual protocols, informed consent forms, participant information booklets, site ART plans, as well as ethics application forms that accompanied protocols when these were submitted to RECs, as well as letters of correspondence to and from RECs (forwarded from participating sites). These documents were not drafted using the rich dense perspectival language used by interviewees, however, they comprised a useful source of information about the controlled language used in more 'official' documents. For such documents, annotations were made according to the party referred to (volunteer, actual participant, participating community) and need being referred to (HIV, sexual and reproductive health care, other) and assigned first-level practice codes. These were subsequently clustered according to whether they appeared to service scientific/ safety purposes or helping purposes. It was not clear initially

which master themes coded documents would inform, however, they were subsequently used to inform the master themes '*Reconciling*' and '*Privileging*'.

#### 3.3.9.8 *Step 8: Continuing coding of subsequent interviews*

Codes from previous interviews were used to orientate the coding of subsequent interviews, while additional codes were added (or elaborated) in line with recommendations to identify repeating patterns as well as newly emerging issues (Quinn Patton, 2002a; Smith & Osborn, 2008). This allowed the development of a successively integrated list of codes (cf. Willig, 2008) that tried to reflect an open mind while recognizing the inevitable influence of previous coding (cf. Lavie & Willig, 2005). The process described above was undertaken for transcribed interviews with representatives from other stakeholder groups.

#### 3.3.9.9 *Step 9: Continuing to structure codes into subthemes and master themes*

As set out in an earlier step, tables for every interview continued to be developed setting out coded extracts clustered into code-clusters (sub-themes). Also master theme tables continued to be developed that meaningfully encapsulated various sub-themes (cf. Alexander & Clare, 2004, p. 74). Master theme tables contained all the codes, quotes and participant identifiers, clustered into several sub-themes from across all interviews. These master theme tables were not merely visual representations of prior coding and clustering. Rather, they enabled that process to take place more precisely. Working with these master theme tables allowed a detailed examination of each text-extract tagged with the same code, and convergences and divergences between them. This was akin to 'analysing codes' (Braun & Clarke, 2006, p. 89). Considering the relationships between codes, sub-themes, and master themes led to some reorganizing and renaming aspects of the coding structure at this point. Sub-themes are considered useful for giving structure to large and complex master themes (cf. Braun & Clarke, 2006). In this analysis, each master theme comprises of four or five sub-themes nested within the master theme. This was akin to grouping together closely-related sub-themes into higher-order themes (cf. Clare, 2002) or identifying where a higher-order theme encapsulates lower-order themes meaningfully (Alexander & Clare, 2004). In Appendix 4, there is a summary of codes clustered into subthemes and master themes.

The twenty-one interviews plus six additional transcripts provided the co-researcher (as set out earlier) formed the primary information for this analysis. Supplementary data comprised text excerpts from additional interviews on prevention modalities conducted by a co-researcher where care-related concerns were mentioned.

It has been noted that there is no correct number of participants for a qualitative study (Smith & Osborn, 2003 in Brocki & Weardon, 2006). The danger with larger samples or a large analytical base is losing subtle meaning inflections (Smith & Osborn, 2003, in Brocki & Weardon, 2006). This danger was countered by generating detailed codes that would capture subtly different manifestations of the sub-themes to provide for sufficiently textured over-arching themes.

Following the steps outlined above led to the development of three over-arching themes fairly smoothly. It took much longer to develop two other over-arching themes. The over-arching themes did not all develop simultaneously.

#### 3.3.9.10 *Step 10: Naming master themes*

In order to find a name that seemed to capture the overall quality of the over-arching themes, the overall structure of the master theme tables was examined and various titles were experimented with to see how well they rendered the texture of stakeholder experiences. For example, for the theme ultimately entitled '*Privileging*' the title '*Seeing differences*' was originally assigned, revised to '*Adjudicating differences*' because it seemed that many of the sub-themes were concerned with perceived differences between various parties, for example, between participant and citizens, or between participants at one site versus participants at other sites. However these titles seemed too neutral - as if the experience was merely about noticing differences or managing them somewhat clinically - whereas many sub-themes captured ambivalence between interviewees, and within interviewees, about advantaging some parties over others – an overall quality of their experience that was more effectively captured by the title of '*Privileging*'.

### 3.3.9.11 *Step 11: Writing master themes into a narrative*

At this stage the researcher is encouraged to write a detailed description for each theme (Braun & Clarke, 2006) and translate the themes into a narrative account where these are illustrated and nuanced. It is recommended that visual aids are used to generate an analytic commentary interspersed with verbatim extracts (Braun & Clarke, 2006; Smith & Osborn, 2008). The researcher should provide a convincing account of the nature and quality of the participants' experience of the phenomenon under investigation (Willig, 2008). The researcher should identify the story that each master theme tells and how it fits into the broader overall story being told (Braun & Clarke, 2006).

The five master theme tables were used to structure a narrative account. This was developed by moving back and forth between the data as represented in the master theme tables and the narrative account to assess whether all the sub-themes were being adequately represented. This was considered a 'conceptual web' including larger meanings and their constitutive characteristics (Miles & Huberman, 1994, p. 63). Quotes were selected that supported the analytic point (cf. Braun & Clarke, 2006) and that represented the most articulate expression (Brocki & Weardon, 2006). 'Editorial elision' in quotes was represented by using the convention of (...) (Smith, 1999, p. 286).

At this stage of writing up the narrative account cycling back to earlier stages took place in the form of checking whether text had been accurately coded and meaningfully clustered. This reflects the observation that analysis is recursive, not linear, where the researcher has to move between coded data extracts and the analysis being written, and that writing is an integral part of analysis (Braun & Clarke, 2006). All the data extracts were examined to check if they were collated systematically in relation to a particular sub-theme and in relation to an overall master theme (cf. Braun & Clarke, 2006) to make sure that constituent sub-themes as well as emerging master higher-order integrative themes were grounded in the transcripts (cf. Willig, 2008).

#### 3.3.9.12 *Step 12: Considering 'saturation'*

Saturation is sometimes defined as when no new information emerges (Fossey et al., 2002) or as when no new relevant knowledge is being gotten from new interviewees (Tong et al., 2007). In this study it was possible (after each interview) to develop new first-level codes, even up to the last interview, however, the subtheme that this was an instance of ceased to be new, that is, new first-level codes could always be accommodated under existing code-cluster or sub-themes.

Saturation has also been defined as when no new themes emerge from the data (Brocki & Weardon, 2006) or when themes are 'fully developed (...) patterns are recurring' (Fossey et al., 2002, p. 726). It is also defined as the stage at which further observations yield minimal information to challenge or elaborate the conceptual web of codes and themes that the researcher has developed (Giacomini & Cook, 2000) and when researcher thoughts about the data do not add anything new to the understanding that has been developed (Kelly, 2006c). These latter definitions more accurately captured the experience in this study. It has been noted that the process of examining old extracts in the light of sub-themes and master themes and emerging insights could continue indefinitely, therefore, the researcher should rather strive to recognize when an analysis represents understanding in a way that is coherent and integrated while retaining nuances (Elliot et al., 1999).

#### 3.3.9.13 *Step 13: Checking if themes were internally consistent and distinct*

The researcher is encouraged to check whether data within a theme coheres together meaningfully (Patton, 1990 in Braun & Clarke, 2006) and whether aspects of a theme cohere around a central concept (Braun & Clarke, 2006), and whether the theme has internal consistency. In addition the researcher is encouraged to check whether there are clear and identifiable distinctions between themes (Patton, 1990 in Braun & Clarke, 2006) and to avoid too much overlap between themes (Braun & Clarke, 2006). After such a review, it was clear that one sub-theme (code-cluster) was nested under more than one master theme – because it informed the understanding of several over-arching themes. Flowers et al. (2000) note that themes can be inter-related, and in this account, such inter-relatedness stemmed from code-clusters that were accommodated under more than one over-arching theme.

#### 3.3.9.14 *Step 14: Interpreting master themes*

It is recommended that the researcher should offer some interpretation of what it means for the participants to have the concerns that they do (Reid et al., 2005). This requires a move from participants' accounts to the researcher's account of participants' accounts (Sandelowski, 1998). The researcher should interpret themes drawing on theoretical concepts and formulations (Willig, 2008; Larkin et al., 2006) and locate participants' experiences in the theoretical literature (Green et al., 2007). In this study major themes were discussed in terms of current ethical frameworks and ethical guidelines, and guiding questions included: what is the ethical significance of this theme? (cf. De Vries & Van Leeuwen, 2010) or in what way does this theme indicate a new ethical problem or a new nuance requiring attention? (Draper & Ives, 2007; Solomon, 2005 in Sugarman et al., 2007) or in what way does this thematic data show how recommendations could be reframed to be viewed as more relevant or responsive? (cf. De Vries & Gordijn, 2009).

### 3.4 **STUDY QUALITY**

It has been recommended that qualitative researchers consider various strategies to enhance the credibility of their research and report such credibility-enhancing strategies (Creswell & Miller, 2000). It is noted that perspectives on enhancing the quality of qualitative research vary depending on the preferred qualitative paradigm (Cohen & Crabtree, 2008). This section reports on processes used to strengthen the overall credibility of this study.

#### 3.4.1 **INCLUDING A REFLEXIVE ACCOUNT**

In general qualitative researchers are encouraged to become self-conscious about (Giacomini & Cook, 2000) and to self-disclose a range of possible influences as a credibility-enhancing procedure (Creswell & Miller, 2000). Researchers should acknowledge their theoretical orientation (Elliot et al., 1999) that influenced how the problem was formulated and the material considered relevant (Malterud, 1993). They should try to expose or give details about

their preconceptions (Malterud, 2001) and their initial beliefs or anticipations about the topic (Elliot et al., 1999).

They should acknowledge their reasons for engaging in the current study or motivations (Cohen & Crabtree, 2008) based on practical experience or personal involvement in the actual subject matter (Malterud, 1993). They should disclose their training, previous personal and professional experiences (Malterud, 2001), occupation (Tong et al., 2007) and relationships with participants (ibid). They should try to establish the effects of such factors on what they investigated, 'the angle of the investigation', and how the research question was explored (Malterud, 2001, p. 483; Tong et al., 2007). They should also declare these factors so that readers themselves can assess the impact on the interpretations (Tong et al., 2007). This was addressed in previous sections rather than in a separate section here.

#### 3.4.2 **MAKING USE OF TRIANGULATION**

It is recommended that researchers try to enhance the validity of their account by making use of multiple and different sources of information (Van der Riet & Durrheim, 2006) to form codes and sub-themes and major themes thereby not relying on a single incident or data point (Creswell & Miller, 2000) but rather relying on multiple information sources (Giacomini & Cook, 2000). The aim here is to get information from different sources (people, documents) in different ways (interviews, document review) in order to illuminate various facets of an issue (Fossey et al., 2002).

Notably, the objective of triangulation is not necessarily to get convergence or agreement between different information sources but rather to enrich the description and understanding of a phenomenon (Malterud, 2001), to solicit more 'grist for the research mill' (Quinn Patton, 1999, p. 1192) and to get a broader, more complex understanding (Tong et al., 2007). Triangulation is less useful as a way of trying to converge on a 'single consistent account of a phenomenon' than 'as a method of enriching understanding of a phenomenon by viewing it from different perspectives' (cf. Flick, 1992 in Yardley, 2008, p. 240). The previous section set out that various and multiple interview sources were used to explore ancillary care (cf. Quinn

Patton, 1999) for example site staff, REC representatives and CAB representatives and other major interest groups. Document review was also used to explore the phenomenon of ancillary care (cf. Fossey et al., 2002) in addition to interviews.

### 3.4.3 MAKING USE OF MORE THAN ONE RESEARCHER

It has been recommended that making use of more than one researcher can strengthen the credibility of a study. The value lies in the way that multiple researchers can 'supplement and contest' the other's statements rather than aiming for consensus across researchers (Malterud, 2001, p. 484). This has been referred to as triangulating perspectives (Yardley, 2008). I coded the data and discussed emerging first-level codes in repeated meetings with other members of the team who read certain transcripts which helped to modify and clarify codes (Yardley, 2008). Two other researchers also coded a portion of the interviews and codes were compared and discussed in subsequent meetings to inform the development of a modified coding scheme. My supervisor also checked the analysis and interpretations as recommended by Brocki and Weardon (2006). The aim was to strive to develop a deeper, more complex understanding (cf. Tracy, 2010).

It is argued that making use of more than one researcher to code does not aim for 'a single definitive reading' but rather to verify if the coding and analysis has been systematically undertaken and is supported by the data (Osborn & Smith, 1998, p. 69). It aims to search for insights from how two people look at the same data (Quinn Patton, 2002a). Yardley (2008) argues that if the researcher's approach is interpretative, then strict inter-rater reliability checks are not appropriate, and if two people code data in exactly the same way, this merely shows that a code list and training process has 'enabled them to share one particular perspective on the data' (p. 249).

#### 3.4.4 LEAVING AN AUDIT TRAIL

It is recommended that qualitative researchers ensure that the finished product contains an account of what was done and why (Braun & Clarke, 2006; Flick, 1998 in Yardley, 1998). This is referred to as tracing the analytic journey from raw data to the final analysis (Eatough & Smith, 2006). This involves informing the reader about the thinking that went on behind the transformation of data into results and interpretations (Dickie, 2003 in Reynolds, 2003) as well as documenting data analysis activities (Creswell & Miller, 2000). Koch and Harrington (1998) refer to this as sign-posting to readers what went on during data analysis, so that the reader can decide for themselves whether the final account is believable or plausible (Koch & Harrington, 1998) and whether the conclusions are anchored to the data from they were derived (Malterud, 1993).

More concretely, it involves helping readers to understand how patterns were identified and help them verify the data, its analysis and interpretation (Cohen & Crabtree, 2008). It involves revealing the influences on pattern recognition and the researcher's choices in the development of codes, sub-themes and major themes (Green et al., 2007; Malterud, 2001). Elliot et al. (1999) recommend that researchers set out how they analysed data with concrete examples of codes, subthemes and themes. This helps to reassure the reader that the researcher is not projecting 'fantasies' onto the participants' meanings (Reynolds, 2003, p. 552). If the reporting of analytic procedures is extensive enough, it allows the reader to act as a kind of auditor (Elliot et al., 1999) or enables other researchers to potentially follow the processes (Giacomini & Cook, 2000). Researchers are discouraged from using short stock phrases such as 'themes emerged' or invoke the computer package used to store, organise and retrieve material but instead they should present a detailed account backed up with examples (Green et al., 2007). Smith et al. (2009) note that this helps potential auditors establish that the account was produced systematically and not that it *the only* credible account that can be produced.

The previous section described how the data was coded, clustered into code-clusters (sub-themes) and then organised into master themes. That is, efforts were made to show how the evidence emerged by reporting the route as well as resolution (Kelly, 2006c). Appendix 4 is a

summary of codes clustered into constituent themes, which themselves are structured into master themes.

#### 3.4.5 **AIMING FOR A RICH DETAILED ACCOUNT**

Another credibility procedure involves presenting a dense, detailed account; by setting out the subthemes, and main themes in rich detail (Denzin, 1989 in Creswell & Miller, 2000). Tracy (2010) refers to this as providing a detailed account of study participants' performances and their significance. In the results section that follows, a rich substantive account is presented with clear evidence for assertions (cf. Cohen & Crabtree, 2008). The results section also avoids the situation where the questions asked in interviews represent the generated themes (cf. Braun & Clarke, 2006).

It has been suggested that researchers should not generate themes from a few coded examples, but should ensure that themes arise from a comprehensive and inclusive coding process (Braun & Clarke, 2006). At the same time, whether codes appear frequently would be only one indicator of their salience (cf. Smith et al., 2009) insofar as single comments can express what is difficult to voice or hard for others to spell out (Willig, 2013). Furthermore, the chief property of words is not that there are more of some of them than others (Miles & Huberman, 1994). In this study, themes were generated not only from frequently coded text but also from how they illuminated some aspect of the account, in order to do justice to the content and complexity of meanings and not merely to measure their frequency (Smith & Osborn, 2008).

#### 3.4.6 **INCLUDING VERBATIM EXTRACTS**

Brocki and Weardon (2006) noted that providing verbatim extracts allows the reader to assess the interpretations made and highlighted the 'centrality of quotes as a form of evaluation in qualitative research' (p. 27). They noted that extracts are selected as examples of a (sub) theme and the extract selected often represents the most articulate expression

(Brocki & Weardon, 2006, p. 97). In the results section that follows quotes are included in response to the recommendation that enough verbatim evidence from study participants be provided to enable readers to interrogate the results (Osborn & Smith, 1998).

### 3.4.7 LOOKING FOR DIS-CONFIRMATORY EVIDENCE

Themes were developed that captured meanings attributed by participants to their experiences (Willig, 2013) however, as a way of enhancing credibility, it was important to look for evidence that disconfirmed sub-themes or major themes (cf. Creswell & Miller, 2000) or sets of patterns (cf. Yardley, 2008) or showed how patterns are contradicted (cf. Braun & Clarke, 2007). It is acknowledged that the sample will not have the same experiences so the researcher needs to account for exceptions (Green et al., 2007) and that different participants may manifest the same over-arching theme in various, non-identical ways (cf. Smith et al., 2009). This is line with the view of reality as multiple and complex (Creswell & Miller, 2000) and reassures the reader that all the data are accounted for and not only parts that fit the researcher's viewpoint (Yardley, 2008).

Under most over-arching themes, codes were generated that were specific enough to capture the nuances of participants' experiences, and to capture a distinct manifestation of the over-arching theme. For example, under the over-arching theme of '*Reconciling*' which generally shows how site-staff understand many of their actions as reconciling scientific and helping functions, there is a single but significant code-cluster (sub-theme) that accounts for their experiencing conflict (a clash) between scientific responses and helping participants with their important health needs. As another example, under the over-arching theme of '*Line-Drawing*' which accounts for how stakeholders accept their actions as a form of limit-setting, there is a single but important code-cluster (sub-theme) that accounts for their experiencing self-questioning around whether their actions were sufficient.

### 3.4.8 SOLICITING MEMBER-REFLECTIONS

Brocki and Weardon (2006) argue that soliciting feedback from participants about the analysis is another strategy for enhancing credibility of the final account. This involves a 'checking back' with study participants regarding the emerging account (Alexander & Clare, 2004, p. 82). However, Cohen and Crabtree (2008) argue that the purpose of data analysis is to organise 'individual statements into themes that produce new, higher-order insights' therefore 'individual contributions may not be recognizable to participants and higher-order insights might not make sense' (p. 335). Koch and Harrington (1998) also argue that it can be difficult for individual respondents to identify their contribution because individual statements are subsumed under various themes. Participants may not be well-placed to confirm more theoretical interpretations (Kelly, 2006b) or latent and suppressed themes (Yardley, 2008).

At the very least however it has been argued that this strategy can help to identify if gross factual errors are present (Giacomini & Cook, 2000) and if study participants' views are being misrepresented (Yardley, 2008). Another view is that this presents the opportunity for new information that throws more light on one's emerging understanding which can act as a spur for a richer analysis (Boor, 2001 in Tracy, 2010). It has also been asserted that the researcher can discuss aspects of the account with not only the original informants but with representatives similar to them (Elliot et al., 1999). In this study, efforts were made to discuss preliminary findings with representatives of major interest groups at a national consultation. I presented a description of the ancillary-care practices adopted by stakeholders as well as key perspectives. This enabled these representatives to confirm the credibility of the information (cf. Creswell & Miller, 2000) and ensured that practices and perspectives captured in first-level codes could be confirmed by the consultation attendees (cf. Fossey et al., 2002; Kaiser, 2009), however, master themes and a more theoretical rendering was not presented to these stakeholders. Fresh information was yielded that assisted to help with the refinement of certain sub-themes under the master theme of '*Privileging*'. This national feedback meeting also reflected efforts at results dissemination, in line with prevailing ethical recommendations (UNAIDS/AVAC, 2011).

### 3.4.9 **CONSIDERING IMPLICATIONS BEYOND THE SAMPLE**

Qualitative researchers should consider the 'extent to which interpretive account can be applied beyond the study context' (Kelly, 2006c). They can aspire to the situation where 'the insights derived from studying one context would prove useful in other contexts that had similarities' (Johnson, 1997 in Yardley, 2008, p. 239). The researcher should describe the participants (and their circumstances) to help readers judge the range of persons and situations to which the findings might be relevant (Elliot et al., 1999) including their own situation (Tong et al., 2007). Researchers should also set out the methods, findings and interpretations extensively enough for readers to determine their applicability to other settings (Green et al., 2007; Kelly 2006c) or use in other settings (Tracy, 2010). The previous section describes the method followed in some detail, and sets out the sample characteristics to help readers to judge the ability of the account to generate answers in other contexts (Kelly, 2006c) so that the results are merely seen as self-referring (Tredoux & Smith, 2006). It is hoped that this study will provide insights that may be helpful, or have relevance, in other contexts or settings with similarities to this one.

Qualitative researchers can also consider theoretical generalizability where links are made between the findings of the study and claims in the existing literature. Smith and Osborn (2008) argued that the power of a study is assessed by the light it can shed in this broader context. This is akin to aiming for a study that is intellectually implicative for other scholars by providing data that extends conceptual understanding (Tracy, 2010). In the discussion chapter, and conclusions and recommendations chapter, implications of this study for ancillary-care scholarship are considered.

### 3.5 **STUDY LIMITATIONS**

The approach adopted for analysis in this study sees participants' accounts as expressions of personal beliefs rather than linguistic devices that are interactively constructed (Osborn & Smith, 1998) It can be argued that IPA (and even the Thematic Analysis) neglects the performative aspects of talk (the way language constructs the world) (Eatough & Smith,

2006) and fails to engage with the constitutive role of language (Willig, 2008, p.67). Put another way, critics have argued that it assumes the 'representational validity' of language - that language provides participants with the tools to express their experiences - (Willig, 2008, p. 67) and it focusses on the meanings assigned to people's experiences rather than the tasks being achieved by verbal statements (Flowers, Smith, Sheeran & Beail, 1998).

In the approach adopted for analysis – namely Thematic Analysis informed by IPA - a multi-stage process was used that did not strictly comply with the guidelines recommended in either approach. Qualitative researchers are encouraged to adapt guidelines (Brocki & Weardon, 2006) and it is recognized that a cook-book approach is not desirable (Smith, 2004). However, one facet of IPA that was least faithfully adhered to was the preservation of individuals' accounts so that a tracing of individual participants throughout the analysis would be possible (Smith, 1999). However, in the results section of the thesis - which follows here – efforts are made to accommodate variations while illuminating what is shared (Collins & Nicolson, 2002; Reid et al., 2005). Some studies using an analytic approach informed by IPA do show fairly large sample sizes (Smith & Osborn, 2008) sometimes over forty participants (Brocki & Weardon, 2006).

Representatives from referral sites providing care services to participants were not invited to take part in this study because of current domestic requirements that research in public healthcare facilities be reviewed by a Provincial Health Research Committee, which would impose unreasonable delays. Actual trial participants enrolled in HIV vaccine trials were also not approached, because this would have necessitated review by additional committees at the level of the coordinating network, imposing delays and constraining implementation of the project. It was hoped that CAB representatives might represent views similar to those advanced by trial participants, but there is no guarantee this was the case. It was not possible to secure participation from representatives of the sponsor organisation, which precluded canvassing their views about ancillary-care concerns, including regulatory restrictions on using research funds for care. It is likely that the perspectives of these key groups would have enhanced the overall study, however, there are often compromises between achieving maximum validity and the costs of doing so (Tredoux & Smith, 2006). These limitations are also revisited again in the final chapter under recommendations for future research.

## CHAPTER FOUR

### RESULTS

This chapter sets out five master themes (comprised of several sub-themes) as developed in the analysis described in the former chapter. These master themes capture meanings attributed by vaccine stakeholders to their experiences. In the subsequent chapter, vaccine stakeholders' experiences are located in the existing theoretical literature about ancillary care.

#### 4.1 RECIPROCATING, ENGAGING, BENEFITTING

*'...these people stand up and be counted...'*

This master theme sets out the manner in which vaccine stakeholders made sense of researcher responsibilities to assist participants with their medical needs. It sets out how stakeholders framed obligations to help participants and how they characterized why 'extra-scientific' helping-based responses should be implemented for participants.

*Firstly*, stakeholders characterized reasons for helping as rooted in a response to participants' contributions, especially in relation to HIV infection. Site-staff and network representatives saw participants as distinguishing themselves from other people, or from the general crowd, by making specific kinds of contributions. They saw participants as 'stepping forward' or 'standing up' - implying that many other persons hang back. These characterizations promote the idea that participants single themselves out for a certain kind of attention from researchers:

*...people who seroconvert on a HIV prevention trial have basically said, 'Ok, you know, I'm going to go on this regimen to see whether we can prevent HIV,' and whether it's a*

*microbicide or a vaccine or anything, you know, these people, you know, stand up and be counted. Much in the same way, we should make sure that if they do get HIV-infected that they have access to the best care that they can get in their region [p/HIV] [c4, site-staff, site B].*

Site-staff and network representatives viewed participants as 'bringing', 'giving' or 'putting in' various things or making various contributions. Stakeholders did not share identical understandings of what has been contributed, and they variously characterized that participants bring their passion, time, effort, energy, commitment, and volunteerism. Therefore, they saw participants as bringing valued, significant, non-trivial things to the table. As one site-staff representative put it:

*...we've asked them to join the study and they're really putting a lot of effort into vaccine trials. I don't think I would be a good vaccine trial participant, they're really putting a lot of effort and a lot of their time and energy to actually be a part of the trial that I think that from the site's side it's important that we try and make it as easy for them if they do become HIV infected and especially being there to support/ to be able support them [p/HIV] [c15, site-staff, site E].*

Site staff and network representatives also held the view that participants take on many risks by agreeing to receive experimental HIV vaccines, including putting their bodies at risk by agreeing to take vaccine products. A key component of this view was that participants make the noteworthy and valuable contribution of willingness to assume risk.

Furthermore, these contributions were viewed as being made (in most instances) to science, to the research, or to the trial, or to the researchers. They perceived that it is the research(ers) that have solicited participants' contributions, or requested participants to make these contributions – so it is to researchers that the participants bring their contributions. In fewer instances, they viewed the contributions as being made to a faceless group of future beneficiaries of the research ('humanity' as one interviewee put it). They characterized these contributions as unforced - they are 'volunteered', or willingly offered in response to requests.

These contributions were seen as being made in the face of highly uncertain personal benefit from the experimental HIV vaccine itself.

Site-staff and network representatives and even some REC members rooted responsibilities to participants with HIV needs in how participants 'take it on the chin' for the research(ers). They saw that participants are owed something in return because participants make contributions - largely on the invitation of researchers. Responsibilities were viewed as responses to offerings received from participants. Site-staff, network representatives and RECs all invoked this central idea that participants contribute some valued thing and that necessitates that researchers give some kind of 'return', or make some kind of helping response. As one network representative stated:

*.....the very nature of our clinical trials is trying to identify individuals who are at highest risk for acquiring this disease who then have you know sort of given their bodies to the clinical trial for an experiment that we don't know will work or not, you know the inherent equipoise that we're in and there being a willingness to do so for more the benefit of society and humanity than for individual bodies and I understand not all individuals are so/ are driven by...what's the word? not philanthropic but are not necessarily driven by these humanitarian impulses. There's an element to it I mean for everyone on some level and there's an obligation to do the most we can for those who do become infected in these clinical trials and especially with the advances that we have, it's really a payback you know that is a real, at the same time, obligation and honour to provide [p/HIV] [c14, network].*

This first sub-theme ('*reciprocating for participants' contributions*') captures the viewpoint that researchers are relating to participants in a way that is quite specific – researchers make an invitation, participants respond to the call, participants make significant contributions, and researchers need to respond appropriately by helping them, especially if they acquire HIV. The helping is understood here – in this first sub-theme – as a kind of giving back. This conception of the relationship was most frequently invoked by stakeholder representatives.

Secondly, stakeholders rooted responsibilities to help participants with their HIV needs in respect for an on-going relationship with participants ('*staying involved with participants*'). They saw that the relationship should not be terminated merely because participants acquire HIV, that HIV-acquisition should not signal the end of the relationship, and they invoked images of not washing hands of participants, and of 'not cutting off', 'not dumping' or 'not dropping' participants. These images characterized *not helping* participants as a kind of 'using and abandoning'. In similarity with the sub-theme above, reasons for helping *were* linked to a relationship with participants, but in contrast to the sub-theme above, reasons for helping *were not* linked to being in a reciprocal relationship with participants. As one CAB representative stated:

*I mean, I think that is a success to say that (the site) has provided/ has planned for the people that 'ok if you come to us, you're not good just because you come with your status that says your negative, you're not only good because you come to us with a negative status and then once something has happened to you, you seroconvert and then we like drop you like that'. No, they have a plan, where they counsel the person, they put the person in (follow-on study) and if that person comes to a state where they need treatment, and then they go to (X) which is the treatment wing. So ya, I believe that is care enough for the people. Cause if the site was only focusing on the negative people, then once you positive then you not their business, that was going to be painful ... [p/HIV] [z3, CAB, site B].*

For these stakeholders there seemed to be something unacceptable about valuing participants only for their HIV-negative status, and they saw helping participants with their HIV infection as signaling awareness of the whole person involved in an encounter with researchers, as evidenced by the following quote:

*...let the human being be treated holistically. You can't zoom into a person to say 'look here, I'm only interested in preventing HIV and AIDS'. You can't divide somebody into segments, ya. So this is why I'm saying that it's important to look at this person holistically. I think it's only ethical and it's only Ubuntu to say 'you are a human being and therefore I'm interested in you. In as much as we are agreeing that you sign informed consent and agreeing that you are only doing HIV preventive trial participation, but still, I'm interested in your wellbeing ...' [p/HIV] [z3, CAB, site B].*

*Thirdly*, site-staff viewed their responsibilities to help participants with their medical needs, by addressing them in a particular way such as providing onsite treatment, as rooted in benefitting or serving participants. They understood that if they adopted a certain approach (or implemented a certain response) they were conferring benefits on participants. For example, they characterized the onsite provision of medication for STIs or even other ailments as protecting participants from time-wasting or stigmatizing attitudes at off-site service-points. The strategy of onsite provision of hormonal contraception was viewed as benefitting participants by protecting them from inadequate counselling, poor toxicity tracking and time-wasting at public-sector referral sites (even while the response of ensuring contraception *per se* was clearly seen as rooted in safety). In this sub-theme, stakeholders did not explicitly anchor responsibilities in the reciprocal exchange, or in a non-using relationship, but they did see that some helping steps should be taken because participants would be assisted with their busy lives, their many non-trivial non-research based demands and their real service needs (*'benefitting and serving participants'*). Interestingly, there were few characterizations that unequivocally grounded STI treatment in a HIV-prevention rationale.

*Fourthly*, and infrequently, site-staff acting as study clinicians anchored responsibilities to help participants with their medical needs in the clinician-patient relationship. They saw that participants should be helped because clinical staff have specialized training in the diagnosis and management of patients' clinical conditions and should respond appropriately using their skills to address participants' health problems (*'caring for patients'*). As one site-staff member stated:

*I think as a nurse or as a doctor you have been trained to screen people for medical conditions and definitely you should refer and if this participant is not already receiving care you should, it is your ethical duty to refer this patient to the appropriate place and make sure that they access care from somewhere (...) the fact that you did the blood pressure and you know, the mere fact that you did the blood pressure you now have an obligation to act on that you know. If you didn't, if you weren't doing the blood pressure its fine and you didn't pick it up and you didn't know the person was hypertensive but the fact that you did it means that you thereafter have an obligation to act on that*

*elevated blood pressure or at least ask them to come back in a week to re-check the blood pressure something. You have to do something... [p/other] [c2, site-staff, site A].*

In summary, the findings captured under this master theme indicate that stakeholders made sense of researcher responsibilities to help participants in very particular ways. (The helping-based responses that researchers actually implemented are outlined in the next theme as well as the final theme). They tended to root responsibilities to help in accounts of the relationships that researchers establish with participants ('*reciprocating for participants' contributions*', '*staying involved with participants*', '*benefitting and serving participants*', and '*responding to patients*'). More specifically, they invoked relationship-centered accounts of these responsibilities. They saw that researchers should help participants with their HIV needs because it represented a 'return' for participants' significant contributions. They saw that researchers should help participants with their HIV and non-HIV needs because it represented relating respectfully in a non-using and non-abandoning way. They recognized providing services as way to add value to participants' lives. They also (infrequently) volunteered the understanding that researchers should help participants because they were clinicians faced with patients. That is, in conceptualizing the duties of researchers to help participants with their medical needs, several relationship-centered ideas appeared to be at work – the first was that researchers were in a reciprocal relationship with participants, the second was that researchers were in a respectful relationship with participants, the third was that researchers were able to serve participants in seemingly modest but significant ways, and the last (and least frequent) was that select research staff were in a clinical relationship with patients.

#### 4.2 RECONCILING

*'...we are providing a better service...'*

The previous theme set out the ways in which these stakeholders made sense of researcher responsibilities to help participants with their medical problems, that is, their interpretations of why researchers should help were delineated. This theme sets out how network and site-staff representatives attempted to adjudicate between their scientific and care roles through

various implicit strategies (how they characterize or understand what they are doing) and explicit strategies (the steps they take to help address participants' medical needs). This theme also sets out subtle conflicts regarding the demands of scientific versus care roles.

Researcher and network representatives characterized many steps to address participants' needs as primarily servicing the scientific business of the trial ('*understanding steps as for science*'). For the condition of HIV, for example, they saw the measurement of participants' CD4 counts and viral loads as necessary to establish the experimental vaccine's impact on disease-progression (for the phase IIB protocol). For the condition of pregnancy, they saw the follow up of pregnancies and infant outcomes as necessary to establish the safety record of the vaccine. For needs such as STIs, they recognized that recording and reporting these as adverse events would help establish vaccine safety. Across a broad range of needs identified in trials, these interviewees made sense of many of their responses by invoking their primary research mission – they were implementing a certain response or practice because it meant rigorous science would be promoted.

Site staff perceived in some instances that the steps they took for science did in fact have certain important collateral benefits for participants ('*understanding steps for science as also helping*'). That is, they made sense of the response they were implementing as primarily serving the scientific interests of the trial; however, they also saw it as having a helping effect on participants in significant ways. For example, some site-staff representatives characterized close monitoring of HIV disease-progression indices to meet scientific objectives in the phase IIB trial as also benefitting participants by early referral for care. In this instance, it was recognised that the primary rationale is scientific, but a striking spin-off benefit was asserted – namely closer monitoring and referral means 'not getting lost' in the system, as evidenced in the quote below:

*...the participant is locked into regular monitoring of their immune system, as well as their virological load, etcetera, etcetera. And these are not inexpensive tests. So, in the public sector, this is not done well you know, it happens infrequently, if at all, and often patients are lost into the, you know, the sort of, chasm of HIV wellness that sort of moments before your positive test and when you need antivirals, and it often is that people will be lost in the cracks during that time, and they turn up back into care when*

*they are almost at death's door, or have some opportunistic infection, or whatever [p/HIV] [c11, site-staff, site E].*

Network representatives and site-staff at all sites implemented a range of explicit responses across a spectrum of needs (HIV, sexual and reproductive, and general needs) that were explicitly 'extra-scientific' in nature; that is, these steps were about helping participants to get their needs addressed in ways that had little to do with promoting scientific integrity ('*taking helping steps*'). That, is, in addition to responses that were implemented to answer scientific questions, many responses were implemented that were about helping participants get the care that they needed. More specifically, for HIV infection, site-staff at all five sites reported providing intensive counselling to participants onsite. Site-staff at all sites reported referring participants for ART to either co-located PEPFAR-funded clinics (three sites) or to the public sector (two sites) following national treatment guidelines, addressing opportunistic infections by referral to co-located PEPFAR-funded clinics or the public sector, and addressing PMTCT needs by referral to public-sector clinics. (They also reported testing participants regularly for HIV using a testing algorithm that excluded VISP but saw this response as grounded in the scientific need to detect true infections, as well as the need to offset complications introduced by the research intervention itself).

Representatives from all sites described numerous steps to help participants to access HIV care, including checking participants' referral preferences, counselling participants to overcome denial and access HIV care, securing participants' permission to share medical information about HIV, sharing letters and medical information with referral sites, reaching agreements with referral sites about sharing information, developing detailed plans for referral, requesting feedback from participants about HIV care at referral sites, and building relations with referral sites by providing training or posting staff and collaborating on educational events. Some sites reported additional practices, for example, booking appointments, alerting referral sites, accompanying participants, and intervening at referral sites.

Network representatives described that dedicated funding had been sourced from pharmaceutical companies for an HIV treatment fund to purchase ARVs for participants who

could not receive coverage through national ART programs, because funds secured from the sponsor to implement the trials could not be used for treatment purposes:

*So there is a fund that [the network] has to pay for antiretrovirals. So if you were sitting in a/ if you were in a situation where there was no access say now there was a clinic in a remote part of South Africa that to get to the HAART clinic it would be impossible you could activate that fund from [the network] to get them to pay for that drugs for you [p/HIV] [c4, site-staff, site B].*

Network representatives also described requiring researchers to develop detailed written plans for addressing HIV at their site (the so-called site HIV treatment plan), assisting with the preparation of such plans (covering initiation criteria, availability of first line and second line regimens, management of opportunistic infections, PMTCT), disseminating best practices to researchers about HIV care, and facilitating ART access between sites – the latter evidenced in the quote below:

*...there wasn't a Department of Health access point near [site X] at the time (...) So we made an arrangement with (PI) at the (site Y) that they would essentially do administration so (site Y) is an ART treatment access point. So they made an arrangement by which they could access and ship the treatment to (site X) so that those people could have access right at the site so that was a case of sort of facilitating to make sure that things were happening but/ and that's happened in other places. So that's another/ that's not really a formal process but it is something that we do [p/HIV] [c10, network].*

Site staff also reported taking steps to address participants' STI, contraceptive and pregnancy needs as well as more general ailments. More specifically, for STIs, site-staff at all sites reported following national syndromic management guidelines, providing STI counselling onsite, and ensuring STI treatment by onsite provision of treatment (four sites) versus referral to public-sector facilities (one site). Sites had implemented various strategies to support onsite provision of treatment, including using a 'site kitty', self-purchasing, or procuring from the Department of Health. For contraception, site-staff reported providing contraceptive

counselling onsite. They addressed contraceptive needs by onsite provision of hormonal contraception, procured from Department of Health primarily (four sites) versus referral to public-sector clinics (one site). For pregnancy, site-staff at all sites described providing counselling for pregnancy options if participants tested positive for pregnancy, referring to public-sector pregnancy services (antenatal services or Termination of Pregnancy), and sharing results with referral sites.

For general ailments (such as anemia, hypertension, respiratory tract infections) site-staff described that they addressed such needs by referral (three sites) versus providing onsite treatment (two sites) and at one of these two sites participants were also referred to *private care* funded by a 'site kitty':

*They are assessed physically, and if there is anything that we cannot handle, we have agreements with the hospital (...) If there isn't/ they are not able to help us, we have the private sector. There's (X) just across the road, it's a private hospital, so, we refer them there and they just send us a bill and then we take care of that [p/ other] [c4, site-staff, site identifier deleted].*

Site-staff at most sites reported soliciting feedback from participants about care received at referral sites. They assessed the functions and capabilities of referral sites and raised awareness about their own capabilities. Many of these responses were implemented by clinical and community-engagement staff hired specifically to take on such functions.

Site and network representatives perceived that when steps were taken to help (that were not strictly necessary for the science) such as providing some care services directly to participants onsite to avoid time-wasting offsite, there are benefits for sites that may well improve scientific outcomes ('*understanding helping steps as soft science*'). This perspective was reported regarding the provision of contraceptive services, treatment of STIs and treatment of general ailments onsite. Site staff characterized some of their helping responses as inadvertently (yet importantly) strengthening the scientific initiative, as shown below:

*Protocol-related is the retention is very good. You've got good rapport with the participants. So you would/ even you data would/ you would collect as much data as you*

*possibly can. And if it's a good relationship, that means there is that openness. We're doing normal, subjective data collection. So, if you've built that rapport with them, it's easier for them to say, 'You know, last night I actually did not use a condom,' so, already, that, because we don't want surprises three months down the line when somebody sero-converts. So we will note it (...) it also helps us in refining the data [p/non-HIV] [c3, site-staff, site B].*

There were also numerous instances where site-staff made sense of some responses as being anchored in both a scientific *and* extra-scientific reason. They appeared in these instances to understand their response as being for a scientific rationale *and* a helping rationale ('*understanding steps as for science and helping*'). Here they did not see the extra-scientific reason as subordinate to the scientific reason, but saw both as critical. For example, site-staff stated that addressing pregnancy-risk by the onsite provision of hormonal contraception helped adherence *and* helped participants secure a more sophisticated responsive service; and that addressing STIs with onsite treatment helped reporting *and* helped participants secure a less judgmental service. Site-staff seemed in these instances to be integrating scientific and non-scientific reasons for adopting a particular response or implementing a certain approach.

Finally, there were a few striking instances where site staff reported taking steps largely to serve science that they perceived to clash with helping participants with their important health needs ('*understanding steps for science as not helping*'). In one instance, a site-staff representative described that participants are offered enrolment onto disease-monitoring protocols (when they are identified as HIV-infected in the phase I trial, or when they reach ART-initiation criteria on the phase IIB trial) and questioned whether this practice might discount participants' potential fatigue at continued trial participation or conflict with participant's real preferences. In another instance, a site-staff representative described steps to provide pregnancy-prevention counselling to participants and questioned whether the site's abortion rate might be evidence of an over-zealous counselling process to retain participants 'on product' (pregnant participants cannot continue to receive product injections). In another instance, a site-staff representative described pregnancy-prevention

responses for participants, as required for fetal safety, and questioned whether these practices might conflict with participants' real reproductive choices:

*And then also for some of the protocols the extended period of contraception makes it difficult because a lot of our participant are in the reproductive age and want to have children at some point. So it's difficult to expect someone to know that 'I will definitely not have children for the next two years' because things may change, relationships may change and so very often there is turmoil between what they've promised to do for the study and what is needed in their personal relationships [p/contraception] [c7, site-staff, site D].*

In summary, the findings captured under this master theme suggest that researchers and network representatives try to reconcile tensions between research and care roles through a number of implicit and explicit strategies. Implicitly, they understand some steps for science as *also being of clinical benefit* to participants, they see that helping responses *also strengthen the science*, and they characterize some responses as having *both a dual scientific and helping function*. They also explicitly take a number of 'extra-scientific' steps to address needs. That is, these findings show that researchers take many steps to address participants' needs that are not merely to advance the scientific objectives of the trial nor to keep participants safe – these are helping practices. These findings under this master theme do not support the view that researchers feel acutely conflicted by the contrasting demands of implementing the research versus helping participants with their health needs however subtle conflicts remain.

#### 4.3 PRIVILEGING

*'...should standard of care in our prevention centres be different..?'*

As set out under a previous theme ('*Reciprocating, Engaging, Benefitting*'), stakeholders made sense of researcher responsibilities in distinct ways – mainly linked to responding appropriately for participants' non-trivial contributions, preserving a non-using relationship with participants, or conferring benefits on participants. These subthemes provided a rationale for treating participants in a particular way distinct from how non-participants might be treated. This current theme sets out the tensions or equivocations experienced by

stakeholders regarding the issue of 'special treatment' for participants in relation to non-participants (both general citizens and citizens who present for screening but are not enrolled).

Certain site-staff held the view that participants deserve something from researchers that citizens do not, however, they seemed uneasy about how much special treatment participants should enjoy. They experienced some ambivalence about this issue that was recognized by them as such (*'questioning special treatment for participants'*). One respondent noted that the national treatment guidelines for ART-initiation had recently been changed to an earlier initiation (at a CD4 count of 350 instead of 200) and questioned whether participants should in fact receive even earlier ART-initiation than general citizens.

*...we've been a protagonist of [earlier initiation] that since, you know, sort of 2004 or 5, so it's long overdue in our books and, you know, they're very important public health moves, so we fully support that. And, I guess it has been a reason for anxiety in the past, in terms of, you know, should our standard of care within our prevention centres be different? (...) because that obviously then provides an inequality that is quite vast you know (...) it does mean that you're creating a 'have and a have not'... [p/HIV] [c11, site staff, site E].*

Many site-staff and REC representatives felt that participants deserve special steps compared to those that citizens might receive, that is, something of a better deal than citizens. However, they were not in agreement between themselves about precisely what was owed to participants. In other words, there was not a uniform view of what was owed to participants or what degree of special treatment they deserved (*'Endorsing special treatment but not agreeing on the response'*). More specifically, some asserted that participants should get closer disease-monitoring than citizens, some asserted that they should get better psycho-social support than citizens, whereas others perceived they should receive care in specialized non-public health care environments. Still others endorsed the view that participants' HIV care should follow national treatment guidelines (identical to guidelines governing citizens) but there should be 'assisted referral' or special steps to link participants to national care (non-identical to steps for citizens).

Representatives from RECs characterized 'assisted referral' as preventing the phenomenon of the 'disappeared participant' –

*I think there we would be more interested in saying, 'Well are they just going to/ are these people just going to disappear into the system again? We should make sure, in some way, whether that's linking directly to treatment services at the same site, or follow up or something. So that we don't just kind of say, 'Oh well, treatment's available, you know. Go find it. Here's a letter' [p/HIV] [c5, REC, jurisdiction over site E].*

Certain REC representatives endorsed the view that following national treatment guidelines for HIV provided HIV patients with sound care:

*I think the provision of treatment regimens that we have available in South Africa currently is reasonable for participants who have not been exposed to drugs previously and do not demonstrate any resistance. The South African guidelines are fairly close to what is the best possible treatment internationally (...) as we're committing people to many decades of treatment complete aligning to good treatment provided by the local guidelines is correct [p/HIV][c20, REC, jurisdiction over site B].*

No stakeholder appeared concerned that special treatment for participants in the form of assisted referral steps (for example, booking appointments or escorting participants to appointments) might make citizens *worse off* but rather that citizens may be excluded from benefits that participants get.

Some site-staff and CAB representatives worried that ensuring special treatment for participants might make citizens too willing to 'cross over' into being participants. They were concerned about whether steps for participants might unduly influence, 'bribe' (or even 'coerce') citizens into becoming participants. Their anxieties here centered on whether the steps taken for participants represented something that was ethically distasteful, insofar that these steps would make citizens want to become participants too uncritically ('*Worrying about the consequences of special treatment*') as exemplified in the following quote:

*Now if you put such things there I don't know whether I should say it but you know it entices people that if you come here you are going to get this and this, it doesn't sound nice. It seems you are bribing people, you are telling people that 'now if you take part in this you are going to get this and this' and then the way I understand it there shouldn't be payment for participation. For a study to be credible, people should not be bought to take part in it, but if you bribe people to come and take part the credibility of the study reduces [p/HIV] [c12, CAB, site C].*

As set out in a previous master theme ('*Reconciling*'), site-staff did in fact see participants as benefitting in ways that citizens do not, stemming either from the research procedures (for example, serial monitoring of CD4s means earlier referral for ART) or from some site strategy (for example, onsite dispensing treatment for STIs or treatment for other ailments means less time-wasting and less stigma) ('*Recognizing some privileging of participants over citizens*'). However, because site-staff were unsure about the degree of special treatment for participants and the impact privileging might have on sound decision-making, they were ambivalent about advertising ways in which participants are treated differently from citizens. They appeared in some instances to endorse a stealth approach where such benefits are omitted from key documents. As one site-staff representative stated:

*I think those are some of the benefits for a participant to be in the study, because, you know, going to the clinic, and just sitting there for just a minor flu, while we can actually provide medication. So, somehow it's also a benefit for that particular person, to be treated here, in the clinic (...) one of the benefits, though we won't put them in the consent form [p/other] [J1, site-staff, site B].*

Site-staff viewed participants as receiving benefits from trial participation, but maintained a relative silence about possible benefits in written materials (both consent forms and protocols). This held for benefits linked to scientific responses, for example, serial monitoring leading to earlier referral, and benefits linked to care responses, for example, onsite dispensing of treatment leading to less time-wasting. Site-staff saw far more benefits for participants than were declared in written materials. Site-staff seemed somewhat conflicted about committing to paper the ways in which participants may be advantaged in relation to non-participants. They appeared conflicted about the acceptable degree of special treatment

for participants versus citizens. They also seemed conflicted about whether declaring special treatment might act as an inappropriate incentive for potential participants, and appeared to address this latter conflict *indirectly* by omitting such advantages in consent materials. (There is more on omissions in written documents under the final theme '*Partnering*').

Site-staff also appeared to manage their discomfort with the privileging of participants in relation to non-participants by other strategies, such as trying to do more for citizens who volunteer but may not be enrolled, and trying to do more for regular citizens. That is, they offset some concerns that participants are prioritized by invoking the various ways in which they also provided some services to non-participants, or helped non-participants with important health concerns ('*helping non-participants*').

More specifically, they took some steps for volunteers who presented for screening but were not necessarily enrolled in HIV vaccine trials. For HIV needs identified at screening, site-staff reported providing counselling onsite, referring for HIV care at co-located PEPFAR-funded clinics (two sites) or to the public sector (three sites) and providing letters and results (but not providing CD4s or viral load measures). Some assisted referral steps were described, but not the range described for participants. The HIV treatment fund was reportedly not available for screen-outs. For STI needs, they addressed STIs by referral to the public sector (one site) versus providing volunteers with onsite treatment (three sites, including both implementing the phase I HVT) and at one site the strategy was unclear. Various strategies were used to support onsite treatment, namely purchasing drugs using a 'site kitty', PEPFAR funds, or procuring from the Department of Health. For contraceptive needs, hormonal contraception was ensured by referral to public-sector facilities (two sites) and by onsite provision of free hormonal contraceptives (three sites). In the main, sites successfully managed to partner with the Department of Health to secure hormonal contraception for onsite provision. For more general ailments (such as hypertension), site-staff reported addressing these by referral to the public sector (four sites) versus providing onsite treatment (one site).

Site-staff at all sites also reported taking a number of steps to help general citizens in the community with some of their health needs. Reported steps from various sites included providing HIV education initiatives, providing HIV testing and counselling services to

individuals and partners, providing screening for TB, providing contraceptive awareness-raising, providing sexual health services, and providing cholesterol, glucose and blood pressure screening.

Site-staff described steps that indicated that participants at different sites were getting differences in the quality of care based on referral-site characteristics or because of the strategies sites adopted to address needs. For HIV needs, site-staff recognized that referral to co-located PEPFAR-funded HIV care has certain advantages over referral to public-sector care. A respondent stated *'our participants are privileged in a way in that they by-pass the public sector rigmarole which is sitting and waiting in long queues for hours, delays in ARVs.* [c2, site-staff, site A].

Site staff also recognized that public-sector HIV care in one province may differ from that in another province, alluding to how quality of care may be differentially impacted by referral site conditions. A representative from a site that refers to the public sector in one province reported: *'we haven't really struggled with very long waiting lists or major problems (...) So, I must be honest, we've never struggled with what I know other sites might have experienced in other provinces'* [c11, site E]. A contrasting report from a site representative that refers to the public sector in another province stated: *'they will tell you 'we don't have this and we're still waiting for this and that' and because of the shortage of resources and human resources well I think that hampered progress ...'* [c8, site C]. Respondents also reported variable implementation of national policy for ART-initiation (that changed from initiation at a CD4 count of 200 to initiation at a CD4 count of 350 over the course of this qualitative exploration). A site representative reported: *'we are referring participants to our local clinics here and they don't have that policy implemented yet'* [c16, site refers to public sector 1]. A contrasting report noted: *'Yes it has been implemented'* [c16, site refers to public sector 2].

Site-staff perceived that certain practices to address needs are associated with certain advantages. For STI needs, site-staff at most sites recognized the advantages of onsite treatment for participants (less time-wasting and less stigmatizing attitudes than at public-sector facilities). Referring to attitudes from public-sector staff, one respondent remarked: *'the nurses, they are too cheeky for (participants). They ask them 'last month you were here with*

*an STI, you came back again, so we are not going to tolerate this thing.” [z4, site-staff, site B].’* (p. 86). For contraceptive needs, site-staff saw advantages for participants of onsite provision of hormonal contraception (more sophisticated counseling, less waiting, better toxicity-tracking). (*‘we are technically also providing a better service for participants’*) [c11, site-staff, site E]. For general ailments, onsite treatment was understood to be an advantage for participants (involving significantly less time-wasting than at public-sector facilities). One respondent noted *‘they will tell you the security guard sent me away. It happens all the time...’* [c2, site-staff, site A] while another stated *‘They sit there the whole day [laughs]. They miss work’* [c3, site-staff, site B]. At one site (as mentioned earlier) participants were referred to private practitioners, and the bill was footed by the site.

Site-staff did not report feeling conflicted about differences in care between participants at different sites (as they did about differences between participants and citizens) and in fact endorsed the need for variable strategies to address participants’ needs (*‘Taking steps that privilege participants across sites’*). Put another way, site-staff declared responses that showed privileging of participants at some sites in relation to participants at other sites, but they did not explicitly frame across-site privileging as a conflict, as suggested in the following quote from a site-staff member at the site where private health-care was utilized for participants (a strategy that was not adopted at any other site):

*So the fact that we are able to take care of them during the follow-ups, as in they access the health system here, it’s something that they like, and I think they talk about it (...) I think, they themselves confess and say, this is/ ‘the whole year I know I have a medical aid’ [laughs] It’s not really a medical aid, but, it is a medical aid...[p/ other] [c3, site-staff, site B].*

In summary, these findings indicate that stakeholders agree that researchers (because of some positive obligation to participants as set out in the first master theme *‘Reciprocating, Engaging, Benefitting’*) should take steps for participants that they do not necessarily take for non-participants, however they did not necessarily agree between themselves on what those steps or responses should be. Some were ambivalent about how much special treatment participants should enjoy in relation to citizens. Some questioned the consequences of special treatment on decision-making. Many recognized there are ways in which participants

are advantaged in relation to citizens, but unresolved questions about the correct 'dosing' of responses or consequences for decision-making, such as 'bribery', or even 'coercion', prevented them from committing these to paper. To offset some discomfort about privileging, site-staff implemented helping steps for volunteers as well as general citizens. They took steps that demonstrably advantaged participants at some sites over participants at others but this was not necessarily experienced as a conflict.

#### 4.4 LINE-DRAWING

*'...people must be reasonable you know...'*

As set out in previous themes, site-staff and network representatives described a range of active steps that they took to help ensure that participants' medical needs were met over and above scientific steps ('*Reconciling*') and they characterized a distinct view of researcher responsibilities to participants ('*Reciprocating, Engaging, Benefitting*'). They also experienced some tensions around participants being advantaged in relation to citizens ('*Privileging*'). The current theme sets out the ways in stakeholders drew limits around responsibilities to review protocols, address needs, and engage participating community.

*In terms of ethical review, REC representatives characterized certain needs as being 'in focus' compared to other needs, portrayed through terms such as 'related to the research', or 'on the radar' or not 'peripheral'. This idea (that some needs are 'in focus') was invoked most strongly in relation to HIV. They used this idea of 'needs in focus' to make *some needs stand out* from the array of needs that might be encountered in review of protocols; and this 'standing out' was rooted in whether the need was connected to the specific research mission. Importantly, REC members did not invoke the idea that HIV was more a serious or more life-threatening need than others, but rather that HIV was at the heart of the business that was bringing researchers into contact with participants ('*understanding some needs as in focus*').*

REC representatives used the idea that some needs are 'in focus' to help them decide on appropriate responses that they themselves should implement. Members of all four RECs (with jurisdiction over all five trial sites) viewed the needs at the heart of the research as deserving more vigilant review, they linked their notions of what to 'look for' to what the research 'looks for', and they reported more scrutiny of plans for HIV needs than for non-HIV needs. They seemed to use the idea of needs 'in-focus' to help them to focus their own activities. This suggests that when needs were seen as strongly connected to the research investigation, they were viewed as somewhat privileged for more demanding review steps ('*understanding needs in focus as deserving more demanding review steps*').

*So with regards to the first stage, the point of review, I have a feeling that it's not very high on the committee's radar, that the committee is not particularly vigilant about whether or not care and treatment will be provided for concurrent conditions or conditions that emerge in the course of the person's enrolment, that's an impression that I have, is that we would be much more concerned about provision of care and treatment for the condition that's the focus of the study rather than related or concurrent or coincidental conditions [p/ HIV/ other] [c19, REC, jurisdiction over site A].*

REC members also perceived that resource constraints (time and attention) must be considered when implementing protocol reviews. They described adjudicating how much time and energy was apportioned to firstly, HIV vaccine protocols versus other protocols, and secondly to ancillary-care concerns versus other ethical complexities ('*invoking costs/ time in review*'). They used the notion of undertaking sound review for all submitted protocols to limit the resources they expended on reviewing ancillary care in HIV vaccine trials. REC representatives did appear to wonder, sometimes, if their responses were totally adequate:

*...there is the human again, tension of watching the time and getting too waylaid by certain discussions and at the moment one tends to spend too much time worrying about one's informed consent forms and you're scared to raise the substantive issues because of the time around the debate so that is a tension [c6, REC, jurisdiction over site E].*

*In terms of addressing needs, site-staff and network representatives saw that they were oriented by a central 'mandate', 'job', 'business', 'goal' or 'mission', characterized as*

answering the scientific question, answering the research question, discovering important knowledge about HIV vaccines, or finding a biomedical HIV prevention intervention. This mission was viewed as significant, valued or non-trivial. They characterized the primary activity organizing their contact or interaction with participants as research (*'invoking the primary mission'*):

*...we only have so much capacity to take care of people as part of this answering this research question and you know once we start layering on different levels of care then ensuring care then you know our job becomes more complex and more burdensome in order to answer the scientific question and the urgent need here is to answer the scientific question and it's sort of a question of/ sort of/ it's a matter of keeping your eye on the ball, for us, and making sure that we are working towards that goal...[p/other] [c10, network representative].*

Site staff and network representatives also characterized some needs of participants as 'inside focus' or 'inside scope' whereas others were not (*'understanding some needs as in focus'*). The status of a need (as 'in' or 'out' of the focus) was used to help decide what responses were reasonable to implement. For example, several interviewees used this concept to help them justify that direct treatment onsite for general health problems was not reasonable. General medical conditions, they seemed to say, fall outside of the research focus so why should we address those needs in that way? (*'understanding needs in focus as requiring more demanding steps'*). As another example, referral was frequently endorsed as an adequate response for non-HIV needs but far more active, assisted referral was frequently endorsed for HIV needs, along with special mechanisms such as the HIV treatment fund.

Furthermore, site-staff and network representatives used the idea of possible damage to the overall research mission to help them decide whether certain helping-based responses were reasonable. They saw that implementing certain responses could make the research 'shut down' or be 'brought down' or be damaged through the bleeding-off of resources or capacity, for example, by diverting of staff attention (*'invoking costliness of certain responses on the primary mission'*). This idea (of not damaging the research) seemed to be used to select reasonable helping-based responses from a presumptive array of possible responses. They understood 'costing' the research initiative too much as an important way of setting limits on

their responsibilities. Here the notion that there are responses that are 'reasonable' seemed to be key (and by comparison there are 'unreasonable' ones). One way they tried to weed out unreasonable responses was by using the idea that reasonable responses do not cost the primary mission too much:

*You know, it's hard enough to conduct research in these settings, without now coming up with a whole plan about what to do for every ache and pain. I think people must be reasonable, you know. One, we're looking for a biomedical intervention to prevent HIV and you know, one can do so much...[p/other] [c4, site-staff, site B].*

Site staff and network representatives understood that there are various ways of 'costing' the research enterprise in terms of the impact on resources (most often staff time and energy, sometimes money, and infrequently shouldering legal responsibility for participants' care) as well as the impact on the scientific integrity of the trial. For example, a site-staff representative questioned whether contraceptive IUDs should be provided to participants (instead of injectable hormonal contraception speculated to increase HIV-risk) given the lack of availability of IUDs in the public sector at the time, the substantial re-training of site-staff that would be required, and their overall cost. (These interviewees recognized that contraceptive mandates were required for safety, but still questioned whether such responses could be implemented more helpfully). Site-staff and network representatives questioned whether participants should be provided with diagnostic-based screening for STIs, given that this may exclude participating sites without closely located laboratory capacity. A network representative questioned whether providing participants acquiring HIV with early treatment would prevent researchers from establishing if the experimental HIV vaccine reduces viral load (a critical secondary endpoint of such trials). This latter observation represents an example of where implementing a response to help participants address their medical needs was perceived to clash with the critical scientific objectives of the trial, as evidenced in the quote below:

*...If we are moving toward earlier and earlier treatment in the course of natural infection, and that treatment/ the recommendations are the treatment be given as early as possible, that would interfere with the potential of measuring any reduction in viral load or disease modification that a vaccine would provide/ any of those benefits. We were concerned about this in (named trial) especially in communities such as San*

*Francisco where the Department of Health in San Francisco have recommended to provide treatment as early possible. That said, most practitioners and most individuals who get infected are more comfortable waiting, you know, rather than going on ART during acute or early infection most of them do wait until their CD4s start dropping. If we haven't seen that yet in San Francisco we're not likely to see it in South/ Southern Africa but it nonetheless will be an issue as more and more evidence emerges that early infection [sic] does reduce longer term sequelae of infection and other peripheral effects of early immunodeficiency...[p/ HIV] [c 14, network].*

In some instances, stakeholders appeared to do line-drawing by invoking the responsibilities of others. That is, they were not necessarily saying 'we don't take this step because it will cost the research too much' but rather 'we don't take this step because it should be taken by someone else'. For example, network representatives described requiring researchers to do detailed written planning about how they will address HIV needs, but they assigned to researchers the responsibility to monitor these plans. Network representatives reported they can assist sites to provide treatment for STIs, but they largely assigned to researchers the responsibility to address participants' contraceptive needs and STI needs. These are instances where the idea that responsibilities are apportioned seemed important. They were recognizing that other partners should also share responsibilities for care-related activities. This issue, and related concerns, is discussed more fully under the next and final master theme ('Partnering').

In some instances, stakeholders questioned whether the approach they had adopted (for participants largely) was the correct approach, or whether they could be doing more. That is, even after they had engaged in various forms of line-drawing such as considering 'needs-in-focus' or considering costs to the research initiative, they seemed to be left with some doubts about where they had drawn the line. They were questioning whether they should in fact be doing more ('questioning approach/ wondering if more should be done'). These instances of questioning whether an approach was correct, or whether more should be done, cut across various needs (HIV, contraception, STIs).

For example, certain site-staff reported unease at initiating participants with HIV on ART using national treatment guidelines when international treatment guidelines recommended earlier initiation. Site-staff were concerned that participants with HIV would not have access to a third-line regimen in the South African public sector, should they fail to respond to first or second line ART regimen. Site staff described providing counselling and HIV test results to HIV-infected volunteers screened-out of trials yet questioned whether they should be providing better monitoring to such persons, in the form of CD4 counts and viral load results. Site-staff questioned whether they should move away from syndromic management of STIs in participants as recommended by national treatment guidelines to diagnostic-screening of STIs. Site-staff questioned whether they should be moving towards different forms of contraception (for example, IUDs) for participants and away from hormonal contraception (especially progestogen-only injectables) routinely offered in the public health-care system but speculated to possibly increase HIV risk. Network representatives described sourcing money for an HIV treatment fund for participants from low-income countries but questioned whether access should be allowed to domestic (US-based) participants, as evidenced in the following quote:

*...we've actually been concerned that because of constrained resources in some of the communities within the US we're now wondering whether or not you know this would be an issue domestically as well, you know - hopefully not - and we're advocating of course within our own communities to ensure that provisions for treatment are not lost you know because of some of the economic constraints within the US (...) You know I'm not sure if it were raised to a level of real worry but it's been raised in our discussions and in hearing from our sites that on the site-level they are concerned that some of the infrastructure and resources to provide care and treatment domestically are threatened [p/HIV] [c14, network].*

These perceptions were sometimes but not exclusively reported in response to questions about current ethical guideline requirements. This experience (of having lingering questions about their approach or whether the approach should be revised) was linked to yet distinct from the experience described under 'Privileging' of having uncertainty (both within and between-person) about the special treatment for participants versus citizens because that experience was about worrying about participant advantaging *in relation to* non-participants

and this experience was about questioning whether the steps being taken were sufficient - quite simply whether more should be done by them (*'questioning approach'*).

Network and site-staff also engaged in line-drawing practices when it came to engaging the participating community or stakeholders more broadly in decisions about care, or consulting them about such decisions. Therefore, they did not only do line-drawing when addressing needs. They perceived some stakeholders as more critical than others for consultation. They used the idea of their primary mission, and not scuppering this mission, to weed out the steps considered reasonable (consulting during protocol writing) from those considered unreasonable (consulting via large-scale meetings before every trial). They did appear to have some nagging concerns about whether their engagement steps were enough.

In summary, the findings captured under this master theme suggest that site-staff, network and REC representatives tried to draw the line or set limits around their responsibilities in non-arbitrary and thoughtful ways (for addressing needs, engaging the community, and reviewing protocols). For addressing needs, stakeholders used important ideas to help them to work out what is reasonable or acceptable in terms of ancillary-care responsibilities. They did not see all needs as equal – that is they characterized some needs as standing out from the array of needs, and this 'standing out' was accomplished by viewing some needs as strongly linked to the research investigation (the business that brought participants and researchers together). They appeared to view these needs as deserving more attention in the form of more demanding responses, both ethical-review responses and addressing-needs responses. Stakeholders viewed certain responses as undermining the research enterprise (which they deemed to be very valuable) and these notions of not-hurting the research were seen as non-trivial ways to set limits on responses. They also assigned responsibilities to partners as a way of setting limits on their responsibilities. Despite using important ideas used to set limits on responsibilities, stakeholders still experienced nagging concerns about whether their responses were reasonable or whether a case could be made they could be doing more. These findings do not support the view that they felt acutely conflicted but that they experience subtle on-going questioning about their approaches.

#### 4.5 PARTNERING

*'...the ball is not only in our hands...'*

As reported under the previous themes, site-staff and network representatives characterized their responsibilities to help participants address their medical needs in very specific ways (*'Reciprocating, Engaging, Benefitting'*), they implemented many responses to help participants with their care needs unrelated to the successful implementation of the scientific protocol (*'Reconciling'*) and they set limits on the responsibilities to address needs and other activities (*'Line-drawing'*). They experienced some tensions around advantaging participants in relation to citizens (*'Privileging'*). This current theme sets out researcher understandings of their relationships with other parties, as well as how they engaged, and were engaged by, various parties to facilitate care and some of the tensions associated with these partnerships.

Researchers perceived that they could not address all the care needs of participants on their own and that collaboration between multiple role-players was required. This constituted their primary motivation for engaging in relationships with other parties orientated to addressing participants' needs. They described numerous practices to engage in relationships focused on addressing participants' medical needs. Many interviewees characterized these relationships as 'partnerships' and generally viewed these relationships in very positive ways (*'valuing partnering'*). They often described the ways in which their partners were aligned with them in a mutually-valued overarching goal. They saw what the unique contribution of the partner could be – what they 'bring to the table' as it were. They recognised their collaborators' capacity or expertise. They saw them as committed to ensuring care for participants. Interviewees showed, however, that subtle tensions existed in these partnerships or collaborations, where they appeared to have experienced (or anticipated experiencing) partners with their own axe-to-grind, or who drop the ball – potentially undermining care for participants, and where it was questioned whether the care-partner could be implementing a better response. In some cases, the collaborators' vested interests were questioned, or their capacity (*'questioning if partner could be doing more'*).

In terms of *site-staff – local service-provider relations*, site-staff reported engaging local providers in a range of practices orientated to addressing participants' care needs. They reported assessing referral-site functions and resources, highlighting the site's functions and core business, reaching agreements with referral sites about sharing information, sharing letters and medical information with referral sites, soliciting feedback from referral sites, retrieving information from referral sites, engaging service-providers to procure STI treatment for onsite dispensing, engaging service-providers to procure hormonal contraception for onsite dispensing, providing training to public sector staff, posting site-staff to assist with service-delivery, and collaborating with public sector staff on educational events.

Site-staff viewed local service-providers as co-contributors to reducing HIV in the broader community through the conduct of joint education campaigns and prevention initiatives. Site-staff also recognized the distinctive contribution yielded by local service-providers who represented an enduring provider post-trial. Site-staff also recognised the commitment of local service-providers to addressing patient needs often under fairly trying circumstances. Site-staff appeared to view the relationship with local service-providers as somewhat organic, requiring and deserving fairly constant contact and interpersonal investment from specially trained site-staff, in part due to shifting personnel in the public sector. Site-staff often constructed the relationship as an exchange or mutually beneficial trade-off or win-win relationship as evidenced below:

*And so, you know, they need to feel the quid pro quo so we make sure that early on they know that there's somebody who could well be coming into their system, and we also make it clear to them that we will be doing the monitoring, and we will be sharing the results with them. So this/ you know every doctor wants to know what's happening to their patients, but in the public sector it's a limited facility and so this we see as a quid pro quo, and it's gone down very well indeed ...I think it's important to be broad in your relationships. So it's not just what do I need? You know, what can you give me? But it's about, how can we do this as a partnership and a dialogue? What can we do for you? (...) We also take on some of their load. You know, they would otherwise have to be providing a whole lot of contraception, STI treatment etcetera, etcetera, and we're down the road and we help that service. So, again, I think there's an understanding, that*

*it's a, it's a joint, health service in many ways (p/HIV/STI/ contraception) [c11, site-staff, site E].*

Site-staff also characterized some local service-providers as holders of myths about the site's abilities, powers, and resources (for example, myths that sites could finance all components of participant's care), requiring myth-busting on their part. Site-staff also described instances where their efforts to adopt a certain approach viewed as beneficial for participants (for example, the onsite dispensing of STI treatment) was not accepted by local service-providers, because it was viewed as duplicating the services of local government, and potentially conflicting with one of the core mandates of local governmental service-providers. Site-staff also recognized various ways in which the local service-providers were not necessarily a strong capacitated partner, invoking narratives of participants' time-wasting in long queues, participants being inappropriately rebuked for presenting with STIs, and participants receiving inadequate counselling in these locales.

Site-staff, in one striking instance, described experiences of being thwarted in efforts to secure sound care for participants by local service-providers who did not timeously implement changes to ART-initiation (raised from initiation at CD4 count of 200 to earlier initiation at a CD4 count of 350) as evidenced in the following quote:

*...it's just you know from our experience so far it's just a pity that you know it tends to stay in in a paper document for very long before it gets implemented. We are referring participants to our local clinics here and they don't have that policy implemented yet (...) So that the issue that you know it gets decided I think at the top level but it takes very long to have those discussions in meetings and stuff to actually filter down to ground level (...) When we do send the participants at the required level or even you know when we/ when we see their CD4s are declining and getting close to the 350 we already send them in with a letter to say 'they're now here you know start preparing for treatment' but we we can't really force the clinics to do that if they still have the instruction to only start at 200. So we do try and put a little bit of pressure on them but I don't know if it's always working. [p/HIV] [c15, site-staff, site E].*

In terms of *site-staff - network relations*, network representatives reported a range of practices to engage site representatives in a relationship that addressed participants' care. These included consulting local investigators about the care approach early on in protocol development, requiring them to plan carefully for endpoint-care, disseminating best practices between sites about HIV care, as well as surveying site capacity to address needs (in preparation for site expansion). Network representatives recognised the distinctive contribution brought to the table by the site investigators – namely their local knowledge of care approaches, successes and impediments, as well as their local connections to service-providers. They generally characterized local investigators as having critical expertise, know-how and resources, on which they relied.

Site-staff were quick to recognise and cite the commitment to care symbolized by the network establishing a dedicated fund for HIV treatment should national coverage fail (given regulatory restrictions on using research funds for care), seeing this fund as tangible (albeit untested) evidence of dedication to addressing participants' HIV needs, as evidenced in the following quote:

*...but within the vaccine trial's network they were very proactive in dealing with this issue (...) I think the vaccine trial's network is very proactive in making sites deal with this, they were very proactive in identifying that there may be gaps for sites and that some sites may have difficulty accessing treatment and so they sought to find a mechanism to provide those funds which I think uh actually is quite remarkable um that they were prepared to make that level of commitment [p/HIV] [c18, site-staff, site D].*

In a few instances, site-staff recognised that the core mandate of the network – to conduct research using sponsor funds within regulatory restrictions – clashed with certain approaches to address participants' medical needs, such securing funds to provide onsite hormonal contraception or treatment for STIs or treatment for more general ailments. At most sites, site-staff reported resolving this tension by explicit strategies such as sourcing funds for medication from private donors or referring participants to off-site care facilities, however, at one site, representatives appeared to resolve this tension by 'stealth tactics' or by a covert strategy – charging the sponsor to open a file and using those funds to cover the purchase of

medication ('*doing covert operations*') – a strategy defended on participant-centered grounds, namely needing to secure good care for participants:

*...we just/ we've structured our costing to deal with things that we need [p/other] [z6, site-staff, no site identifier].*

Network representatives appeared to recognise that there may be limited 'covert operations' implemented to reconcile respect for ring-fenced funding with addressing participants' needs – as set out the quote below:

*Now how they manage that is really up to them. So if they have another part of their organisation by which they can do that evaluation that's not our business. We don't track it to that point so if there's a way that they can separate out the funding so that (...) the support for that comes from another source, that's really not our concern. But our concern is that from all reasonable perspectives that the funding, from all reasonable evaluations that the funding is not being used for anything but research [p/other] [c10, network].*

Site-staff questioned the approach whereby network representatives relied on investigators to address participants' sexual and reproductive health needs, and wondered whether the network should not be doing more to assist them to address these kinds of needs in HIV vaccine trials.

In terms of *site-staff – CAB relationships*, site-staff and network representatives reported a series of practices to engage CAB representatives in care. More specifically, network representatives described involving CAB representatives on protocol-development teams. Representatives from all sites involved local service-providers on the site CAB. Representatives from some sites reported that ex-trial participants were also members of the CAB. Representatives at all sites reported discussing the sites' approach to care with CAB members, and addressing questions from CAB representatives about care. At all sites, CAB representatives were involved in a pre-trial review of relevant *materials*. At some sites, CAB members (or a subgroup) accessed entire protocols, whereas at other sites CAB members accessed materials such as protocol summaries or ICFs. At all sites CAB members were

informed about HIV sero-conversions, however, actual numbers were not presented to all CABs. At most sites, direct access to participants by CAB members was not permitted whereas at one site CAB members accessed participants after signing confidentiality agreements and receiving photo-identification cards.

Site staff recognised the distinct contribution that CAB representatives make in terms of care, namely that they have expert local knowledge about care approaches in the community that can shape better experiences for participants. Here the value of consulting such representatives was endorsed as a way of improving implementation of care approaches. In a one notable instance, however, a site-staff representative questioned the capacity of CAB members to make care inputs that were medically or scientifically well-informed. This perspective, while not widespread, revealed a characterization of CAB members as potential holders of views that are in some way unreasonable and that challenge site-staff to find legitimate ways to reject such inputs. A site-staff representative offered the following:

*Being a research unit we practice evidence-based medicine and we do have, for example on our Community Advisory Board, we've got representatives of traditional medicine. But I don't know them personally so it's a presumption that people would want a wider range of care to give participants access to, perhaps the option of attending a traditional healer or either practices in medicine that are not necessarily evidence-based, and I think that would create a conflict for researchers (...) so I think you would just get this highly variable range of requests of how this should be managed and that's not a problem but I think accommodating all of them will be difficult. And I'm not sure how easily the community will, I almost get the feeling that people will be slighted if we started picking and choosing you know between people what we listen to and what we don't. [c7, site-staff, site D].*

Representatives from CABs reported on steps to engage them in care that mirrored those reported by site-staff. These representatives generally recognised that researchers took steps to help participants with HIV secure care, and they did not question their commitment to care. In some select instances, however, CAB representatives appeared to question researchers' vested interests in running a good trial as undermining how community representatives were engaged for care. More specifically, they saw their own desire to access

participants directly – to get more authentic ‘read-outs’ of participants’ trial experiences – as being blocked by site interests in protecting confidentiality. They seemed to feel somewhat thwarted by site-staff in this regard, as evidenced in the quote below:

*[Participants] not allowed to meet with us, they not allowed to sit with us. If by accident we have a / like once we had a candlelight and we were with them. We couldn't see because there was trial participants and the CAB and the community. We couldn't identify and say this is really a trial participant, this is really a trial participant. If they have issues I mean they do not/ they not given that platform, practically to come, in practice to come and discuss with us. So we just there. As much as we/ through experience of being community members ourselves, as much as we advocate or we discuss those issues, but we discuss them under general, not under the specific (...) I mean the CABs are there to ensure that the trial participants are not abused or exploited on and that they can rely on, that they can discuss with. But on the other side, there's this big word confidentiality which blocks the whole relationship now. It says black and white that you there as an advocate but then again/ in practice the trial participant is not given a chance due to the confidentiality issues that they talk about, that they cannot discuss these matters with the CABs, the cannot meet with the CABs in person. So we don't know when really in practice you become an advocate [z1, CAB, site A].*

In terms of *site-staff and REC relations*, representatives from both groups undertook various engagement practices related to review of care. Researchers reported informing RECs about the HIV treatment fund, they described their plans for HIV care in the protocol, and responded to REC queries about HIV care. REC representatives reported assessing researchers’ plans for HIV care in review, and asking for details about plans for HIV care. Occasionally, RECs questioned the strategy to address non-HIV needs, and investigators clarified this.

Representatives from all affected RECs characterized investigators as having care expertise and saw them as internally committed to participants’ care, namely being motivated and dedicated to achieving good care for participants – the latter viewpoint is evidenced in the quote below:

*You know I mean I think a generalisable statement would be that, I think that/ my impression of the investigators and the investigative team is that they completely want to do the right thing in terms of standards of prevention and standards of care, that I haven't had in my whatever it is [X] years of being the Chair of the committee any acrimonious arguments around standards of prevention issues or standard of care issues and that my sense is that investigators themselves want to be doing the right thing and are willing to put resources into doing the right thing... [c19, REC, jurisdiction over site A].*

Site-staff described RECs as partners or collaborators in two distinct ways – firstly in terms of trying to establish an HIV care approach and secondly in terms of joining forces (on occasion) to leverage trial sponsors to do more, namely where investigators flagged issues of concern for the REC to raise (with their considerable clout). Here these two stakeholders viewed themselves as occasionally aligned in a mutually valued goal – to ‘force’ sponsors to take an action serving participants’ interests.

*...many of them actually come and talk to one or other of the members of the committee and or one of the Chairs in advance of studies. Some of them have actually come to us and said 'look we're going to put in a study, it's being sponsored by [X] or whatever the case may be and we're not completely happy about what they want' and they actually trigger us or flag what they think we/ they would be very grateful if we would have a look at. [c17, REC, jurisdiction over site B].*

Characterizations were largely positive, however, there were subtle clues that the investigator-REC relationship was not devoid of tension. Site-staff and network representatives viewed the core mandate of RECs as the review and approval of protocols. They anticipated that declaring care strategies in protocols might lock them into an approved strategy and prevent them from implementing flexible innovative strategies to address participants’ needs.

*...there's also an assumption in doing so [setting out care strategy] that you will monitor it and you will provide oversight, you will require consistency across all of the sites in a particular fashion. If you prescribe it in the protocol any deviation from that is an actual deviation from the protocol [c14, network].*

Protocols tended to say little about planned helping responses to address participants' non-HIV medical needs, although several statements were made about HIV (See the table below). Supporting documentation (application forms and letters to RECs) also said little about how non-HIV needs would be addressed. Put another way, a review of protocols and supporting documentation indicated that sites mostly did not declare their strategies for how they would address non-HIV needs. As mentioned earlier under the second theme, protocols declared a significantly smaller sub-set of the overall set of helping responses than those reported in interviews, which indicates that site-staff actually did far more to help participants than they declared in protocols and supporting documentation. It is possible that omissions may be strategic – a form of 'staying nimble' when the care approach is perceived as needing flexibility or revision as conditions change. It seems that unless concerns about nimbleness are addressed, then exhortations to get researchers to submit more detailed plans about care strategies may not be successful.

Table 2: Summary of protocol descriptions regarding care steps

Issue	Description
Participants' HIV needs	<p>The phase I protocols described planned steps for HIV infection justified by safety (e.g. <i>discontinuing vaccinations</i>) as well several steps to assist participants (<i>providing counselling, referring for counselling/ ART/ management, developing a treatment fund, developing site ART plans</i>).</p> <p>The phase IIB protocols described steps consistent with scientific objectives (e.g. <i>monitoring viral load and CD4s</i>) as well as several steps to assist participants (<i>referring to medical professionals for treatment, developing site ART plans</i>).</p>
Participants' contraceptive, pregnancy and STI needs	<p>Protocols for both trials outlined steps for contraception consistent with safety concerns (e.g. <i>assessing contraceptive compliance</i>). Protocols did not describe how contraception would be ensured (e.g. onsite provision versus referral).</p> <p>Protocols for both trials outlined several steps for pregnancies consistent with safety (e.g. <i>discontinuing vaccinations</i>). Protocols did not describe how access to pregnancy services would be ensured.</p> <p>The phase IIB protocols broadly described there would be '<i>access to syndromic management</i>' but the phase I protocols did not describe how STIs would be addressed.</p>
Participants' other needs	<p>Protocols for both trials described steps for other needs consistent with assessing vaccine safety (e.g. <i>assessing adverse events</i>).</p> <p>In the phase I protocol, steps to assist participants to access care were declared for only a few select needs, such as cardiac problems (<i>appropriate referrals</i>) and the phase IIB protocols described no steps to ensure access to services.</p>
Volunteers' needs	<p>Protocols for both trials described steps to help volunteers identified as HIV-infected at screening (<i>providing counselling, referring for management</i>).</p> <p>Neither protocol set out how care services would be ensured for STIs or identified pregnancies or other general conditions.</p>

In terms of *site-staff-participant relationships*, site-staff described various steps they implemented to involve participants in their own care, such as counselling participants to report health problems, informing participants about how their needs will be addressed, and counselling participants to access care.

They also informed participants about the care approach in informed consent documents (see the table below) although in some instances, informational statements about care for non-HIV needs could have been clearer. On some occasions, statements were omitted or they contradicted actual strategies implemented at sites. That is, consent forms tended to utilize boilerplate to the effect that participants would be helped to get treatment for their non-HIV needs but that they would not be *provided with treatment for problems unrelated to the study*.

This statement contradicted reported practices in the phase I trial at both of the affected sites (who dispensed onsite STI treatment to participants) and contradicted reported practices at one of the sites (who provided onsite treatment for other conditions). It also contradicted reported practices in the phase IIB trial at four of the five sites (who provided onsite STI treatment) and two sites of five sites (who provided onsite treatment for some ailments).

Table 3: Summary of consent form descriptions regarding care steps

Issue	Description
Participants' HIV needs	<p>The phase I consent forms described steps consistent with scientific objectives (e.g. <i>discontinuing vaccinations</i>) as well as steps to help participants to access care (e.g. <i>we will counsel you about your HIV infection, we will help you get care and support, we will tell you about places where you can get support and medical care</i>).</p> <p>The phase IIB consent forms described some steps linked to scientific objectives (e.g. <i>testing how the body controls HIV infection</i>) as well as steps to help participants to access care (e.g. <i>you will be helped to get treatment for your infection</i>).</p> <p>Supplementary material set out steps to help participants to access care (<i>we will refer you to medical professionals, we will tell you where you will be able to receive care and medications, you will get access to ART according to country guidelines</i>).</p>
Participants' non-HIV/ other needs	<p>The consent forms for both trials stated that participants must agree to birth control, and outlined some steps for pregnancy (e.g. <i>discontinuing vaccinations if pregnant</i>) but made no statements about how participants would be helped to access services.</p> <p>The consent forms for both trials stated the tests/ exams might detect health problems and they stated <i>'you will be helped to get treatment but you will not be provided with treatment for problems unrelated to the study'</i>.</p> <p>Supplementary material set out steps (<i>referral to available counselling, support, medical and treatment services for illnesses</i>).</p>
Volunteers' Needs	<p>The consent forms for the phase IIB HVT stated that screening tests may show a person cannot join but no care steps were outlined.</p> <p>The consent form for the phase I HVT at one site was same as above, whereas the other consent form outlined steps (<i>we will tell you about places where you need to get support or medical care</i>).</p>

As set out partially under a prior theme of 'Reciprocating, Engaging, Benefitting', site-staff viewed participants and themselves as involved in a distinctive relationship but here in this theme site-staff recognized the unique power held by participants, namely, that it is participants (and only participants) who can ultimately co-operate with steps to secure care for them. Site-staff described experiencing some push-back, denial and resistance by a small number of participants (at every site) who would not respond to their efforts to secure care for their HIV infection identified in these trials. In these instances, site-staff experienced the frustration of these encounters – which appeared small in number but large in impact. As one investigator reported:

*...and we have had, participants who have, you know, been heavily in the denial phase, they've gone 'Get out of my face. This is the worst thing you could have told us, we're out of here', and we have/ we have literally, unfortunately watched the participant die, where we have not been able to change that, despite in-depth counselling and that's/ you know, we also live in a/ in a democratic environment where people have*

*constitutional rights to privacy, and we/ you know, if people choose that way, we use every wile and wisdom we can, at our disposal to try and teach them otherwise, but, you know, autonomy prevails [p/HIV] [c11, site-staff, site E].*

In summary, the findings reported under this master theme show that many stakeholders recognized it was essential for various role-players to be involved in participants' care, and that no single stakeholders would be able to address all participants' needs alone. These findings show that site-staff were engaged in relationships with multiple stakeholders in ways that were orientated towards securing care for participants. These findings show that the relationships were primarily viewed as partnerships, where the contribution of the partner was generally strongly recognized as well as their capacity and their commitment. These findings do show, however, that there were certain tensions that characterized these partnerships, where the care-partners' response was questioned. It was recognised that partners had drawn a line (decided to implement one response but not another) but it was sometimes questioned whether partners were doing enough, or whether they should they be doing more.

#### 4.6 SUMMARY OF RESULTS

In summary, the findings captured under the master theme '*Reciprocating, Engaging, Benefitting*' indicate that stakeholders recognized that researchers have a positive obligation to assist participants with their medical needs, and that researcher responsibilities were viewed as anchored in the researcher-participant relationship. That is, in conceptualizing the responsibilities of researchers to help participants with their medical needs, relationship-centered ideas appeared to be at work including that researchers should reciprocate for participants' contributions (the most frequently invoked conception), that researchers should not use and abandon participants, that researchers should confer benefits on participants, and that select research staff (such as study clinicians) in a clinical relationship with patients should respond appropriately using their professional skills. Interviewees did not always agree on what it was that participants have contributed to the research enterprise.

These findings set out under the master theme of '*Reconciling*' suggest that researchers and network representatives characterized some responses for science as also being of clinical benefit to participants, they saw that helping responses also strengthen the science, and they characterized some responses as having both a dual research and helping function. They also explicitly implemented many 'extra-scientific' responses to address needs that were not anchored in advancing the scientific objectives of the trial or keeping participants safe – these were explicitly helping practices. Researchers tried to reconcile tensions between research and care roles through a number of implicit and explicit strategies, however, subtle conflicts remained.

The findings set out under the master theme of '*Privileging*' indicate that stakeholders were of the view that researchers (because of some positive obligation to participants, as set out in the first theme) should take some steps for participants that they do not necessarily take for non-participants, however some were ambivalent about how much special treatment participants should enjoy in relation to citizens, and they did not agree between themselves on what those responses should be. Some questioned the consequences of special treatment on decision-making to enter trials. Many recognized there were ways that participants were in fact advantaged in relation to citizens, but unresolved questions about the correct 'dosage' of special treatment (or the consequences of special treatment) prevented them from committing such advantages to paper. Site-staff took some helping steps for volunteers as well as for general citizens, in part to offset some discomfort about privileging participants. They took steps that demonstrably advantaged participants at some sites over participants at others but this was not experienced as a conflict.

The findings under the master theme '*Line-Drawing*' indicate that site-staff, network and REC representatives perceived that there are limits to ancillary-care responses, and that they tried to set limits around their responsibilities in non-arbitrary ways. For addressing needs, stakeholders used several ideas to help them to work out what is reasonable in terms of ancillary-care responsibilities. They viewed some needs (those strongly linked to the research) as standing out for more demanding ethical-review and addressing-needs responses – even while seeing other needs as necessitating some kind of response. They also saw some responses as undermining the highly valued research enterprise and 'not-

undermining' was seen as a non-trivial way to set limits on ancillary-care responses. They still experienced nagging concerns about whether their own responses were reasonable or whether a case could be made for them to do more. These findings do not support a finding of acute doubt, but rather a finding of subtle on-going questioning of their own approaches.

The findings (under '*Partnering*') show that many stakeholders saw it was essential that various role-players are engaged to secure care for participants, and that no single stakeholders could address all participants' needs alone. Site-staff were engaged in relationships with multiple stakeholders in ways orientated towards securing care for participants. Relationships were primarily characterized in positive ways - as partnerships - where the contribution, capacity and commitment of the partner was generally strongly recognized. In some instances, however, there was questioning about whether the care partner should be implementing better, different responses.

# CHAPTER FIVE

## DISCUSSION

This section discusses the five master or superordinate themes in terms of the existing conceptual and empirical literature on ancillary care, and existing debates about the ancillary-care responsibilities of researchers. The implications for ethical models and ethical guidelines are also briefly introduced.

### 5.1 RECIPROCATING, ENGAGING, BENEFITTING

The first master theme (*'Reciprocating, Engaging, Benefitting'*) explicates the 'pro ancillary care' reasons held by HIV vaccine trial stakeholders (Merritt, 2011, p. 319). This finding shows that stakeholders recognised a strong positive obligation for researchers to help participants address their medical needs and that these stakeholders agreed that researchers have responsibilities centered on promoting participants' well-being or welfare (cf. Richardson, 2012c). This finding shows therefore that most stakeholders endorse that researchers owe participants some helping-based responses, and are not 'ancillary care skeptic(s)' (Richardson, 2012c, p. 199).

This finding can contribute to (but not settle) the debate about why researchers have obligations (Merritt, 2011) by delineating the moral reasons that are relevant from the standpoint of these vaccine stakeholders. This finding shows that these vaccine stakeholders (comprising site-staff, network and REC and CAB representatives) tended to understand responsibilities for researchers to help in terms of the relationship that exists between researchers and participants. That is, they rooted researchers' responsibilities to do something helpful in the relationship between researchers and participants (cf. Richardson, 2008). This suggests that they did not endorse views resting on what one person owes another needing help '*independent* of any special relationship between them' (Miller, Mello & Joffe, 2008, p. 273, emphases mine) but rather endorsed a 'relational' account of ancillary-care responsibilities (Hooper, 2010, p. 709).

MacQueen et al. (2007) found that one key stakeholder (namely community representatives) held views about prevention researcher responsibilities that were anchored in the researcher-participant relationship, but few details were given about these views. This finding shows – for the first time – HIV vaccine-trial stakeholders’ understanding of this special relationship between researchers and participants (cf. Richardson, 2012c) comprising several distinct characterizations.

These stakeholders perceived that researchers should help participants with their HIV needs because participants contribute various significant things (time, energy, willingness to assume risks), which necessitates a reciprocal giving-back on behalf of researchers. They also saw that researchers should help participants with their HIV, and pregnancy needs, because they should not merely use and abandon participants selected originally because of their ‘health’ and who subsequently acquire health conditions but should rather engage with the fullness of their needs. They understood that researchers should respond in certain ways to participants’ sexual/reproductive and other health needs because by doing so researchers will confer meaningful benefits on their own participants (even while they won’t necessarily do such things for general citizens). They also volunteered the understanding that study clinicians interacting with patients should respond to medical needs using their specialized skills and knowledge. These various conceptualizations point to understandings anchored in significant kinds of relationships between researchers and participants.

The first view (*‘reciprocating for contributions’*) roots researchers’ responsibilities in an exchange taking place with participants - researchers make a call for participation in HIV vaccine trials, certain people step up to contribute valued things to researchers as trial participants, and therefore researchers should respond when participants become medically needy. This view resonates with ‘reciprocity’ that was theorized by ethics commentators (relatively early in the debate) as a possible grounding for researchers’ care responsibilities to participants (Macklin, 2006a). ‘Justice as reciprocity’ is also briefly alluded to in leading ethical guidelines as a consideration underpinning ensuring HIV care and treatment for participants (UNAIDS/WHO, 2007; 2012).

Merritt and Grady (2006) outlined that reciprocity is about 'returning good for good' (p. 1792) and that participants make contributions by *accepting risks* and *assuming burdens* in the service of generating benefits (knowledge generation) for future persons, and therefore others 'incur reciprocal obligations to return benefits' to participants (p. 1792). Millum (2010) argued that the idea underlying reciprocity is that participants contribute to a benefit derived by others, and therefore they deserve something in return, and furthermore, it is sponsor-investigators who enlist participants therefore it is they that should assume the burden of reciprocating fairly for participants' contributions. Richardson (2012c) noted that reciprocity is a 'feature of exchange among individuals, typically thought of as involving an appropriate mutuality of benefit and burden' (p. 468).

Lavery (2008) asserted that the resulting gains for interested parties from trials would not be possible without the *willing participation* of participants (emphases mine). He argued that recognition of the importance of participants' *contribution* is relatively poorly developed in research ethics. He noted that NBAC (2001) foregrounded reciprocal justice and recognised the essential contribution of participants to the research enterprise. Lavery (2008) asserted that participants assume *personal risks*, take on *inconvenience* and *uncertainty*, and invest *time and energy* and in return sponsor-investigators should show some meaningful reciprocity. He noted that reciprocity involves recognizing that participants 'represent a *sine qua non* of clinical research' and their contribution is so essential that it calls for 'some special gratitude or recognition, over and above the potential benefits inherent in a given research design' (Lavery, 2008, p. 701). He argued that reciprocity goes beyond the basic requirement that there be a favorable risk-benefit ratio for research procedures or components (perceived by some as guaranteeing enough benefit for participants).

Lavery (2008) was, in fact, exploring the issue of post-trial access to trial interventions. This suggests that there may be many ways to reciprocate for participants' contributions (for example, providing them with post-trial access to an intervention proven effective in the trial) and that reciprocation does not necessarily have to take the form of helping participants with their medical needs. This point is also made by Ulrich (2011) who noted that reciprocity requires return of benefits for participants' voluntary enrolment but reciprocity does not necessarily specify the type of return. Therefore reciprocity could conceivably be fulfilled by

other returns (such as access to study results or products). This finding shows these vaccine stakeholders here were not saying that helping participants with their medical needs is the only way to reciprocate for contributions, but rather they were saying that helping in this way is one significant way to reciprocate for contributions.

These findings illuminate the 'something' (cf. Forbes et al, 2006; Millum, 2010, p. 150) or the 'good' (cf. Merritt & Grady, 2006, p. 1792) that vaccine stakeholders viewed participants as contributing. They saw that participants take on research-related risk, and assume burdens (time, energy) and bring their passion and commitment to the research enterprise. This resonates well with what ethical commentators theorize to be contributed (cf. Lavery, 2008). No stakeholder here spontaneously referred to restrictions that participants face, such as not giving blood or not getting HIV tested at facilities that cannot distinguish between VISP and real HIV infection.

These findings do show that vaccine stakeholders have slightly differing appreciations of what is contributed, or put another way, they do not necessarily completely agree between themselves on the 'good' that is being offered by participants. This suggests that stakeholders may need to come to more agreement *between themselves* of what is contributed if reciprocity-based reasoning is to offer a stable account of why researchers should implement helping-based steps for medical needs. It also suggests that current ethical guidelines should attempt to spell what participants contribute in more detail. There is more on these points in the final chapter.

It is also worth noting that accepted ethical requirements already insist that potential risks and burdens to participants be compensated, either by the possibility of benefit to participants, or benefit to society. That is, requirements contained in popular frameworks and guidelines try to elucidate how researchers should respect the worth of participants (Emanuel et al., 2000; Emanuel et al., 2004). The principle of 'social value' expresses the idea that persons who *dedicate their time* and *assume potential risks* should do so for a valuable question. Furthermore, the principle of a 'favorable risk-benefit ratio' expresses the important idea that reasonable and minimized risks to participants must be outweighed by some meaningful compensating purpose (Litton & Miller, 2005) such as important

generalizable knowledge or direct medical benefit. These findings suggest that these vaccine stakeholders do not see the potential risks adopted by participants as fully compensated by these important reasons but instead view the adoption of potential risks (and the making of contributions) as significant enough or persistent enough to make a call on researchers' care responsibilities. These findings also support the view that stakeholders perceive that the benefits of receiving the experimental HIV vaccine are highly provisional insofar as participants gain benefits only if they are randomized to receive vaccine, sufficiently protected and subsequently exposed to HIV (Grady, 1994; 1995).

Miller, Rosenstein and DeRenzo (1998) have noted the 'more or less explicit quid pro quo' between researchers and participants, where the participant 'trades his or her time, body fluids, inconvenience and often discomfort' in exchange for the hope that research participation will produce benefits (deriving from the experimental intervention and diagnostic tests, as well as 'education' or 'referral') (p. 1451). They asserted that more attention be devoted to this quid pro quo (seen as initiating and sustaining research) including its scope and limits so that the reciprocal exchanges at the core of research can be clarified.

National operational guidelines (SA NHREC, 2012) and international scholarly articles (Grady, 2005; Wendler, Rackoff, Emanuel & Grady, 2002) recommend paying money to participants for their *time* and *inconvenience*, and participants in HIV vaccine trials do receive monetary payment. However, findings from this study suggest that these stakeholders do not view participants' monetary payment for time and inconvenience as sufficiently off-setting all participants' burdens, and perceive that certain burdens remain that require researchers to respond reciprocally by helping them secure care.

This same sub-theme ('*reciprocating for contributions*') also appears to resonate with the factor of gratitude for uncompensated risks and burdens held to be significant in both partial entrustment and whole person accounts of ancillary care (cf. Dickert & Wendler, 2009; Richardson & Belsky, 2004; Richardson, 2007). However, the understandings volunteered here may not necessarily support the title of 'gratitude' insofar as these stakeholders did not

necessarily feel thankful, but appeared to feel obliged or indebted; as such that they could only discharge their responsibilities with a proportional giving.

The factor of 'gratitude for uncompensated risks and burdens' has been explained in various ways. Richardson and Belsky (2004) argued that researchers rely on and benefit from participants *giving them permission* to conduct research and for their *co-operation* with the research. Richardson (2008, 2012c) set out that researchers may owe participants a debt of gratitude for their *willingness* to undergo procedures that may be *risky, painful or inconvenient*. Belsky and Richardson (2004) argued that participants may provide *researchers with a 'hard to come by scientific opportunity'* (p. 1496). For these things, it is argued, researchers have a debt of gratitude which is not fully discharged just because of benefits that may accrue to participants because of their participation in research procedures (Richardson & Belsky, 2004). The factor of gratitude is inherently conceptualized as proportional – the more participants have been willing to do or take on, the more researchers are indebted to them and the more they owe them (Richardson & Belsky, 2004) and it is acknowledged that reciprocity 'gets some grip on the case of research participants in roughly the same way as does the consideration of gratitude' (Richardson, 2012c, p. 123).

The significance attached by these interviewees to the exchange between researchers and participants suggests that vaccine stakeholders may find notions of reciprocity and gratitude for risks/ burdens relevant to their decision-making (cf. De Vries & Gordijn, 2009; Solomon, 2001 in Sugarman et al., 2007). That is, guidance that spells out such justifications may have some traction with these trial stakeholders because it may respond somewhat to their lay ethical notions or intuitions about this matter (cf. Carter, 2009). At the very least such reasoning should not be omitted from frameworks that intend to popularize and raise awareness about ancillary care such as the Four P's (Participants, 2008). There is more on this in the next chapter. It is possible that vaccine stakeholders accorded the need for reciprocity such salience because these prevention trials (enrolling 'healthy persons') lack some of the direct health-related benefits apparent in treatment trials (enrolling 'sick' participants). This issue could be explored by detailed qualitative work comparing stakeholder views across various trials and studies. It is possible that in other trials or studies, stakeholders may attach more salience to other rationales or other factors advanced by models of ancillary care, and assign reciprocity more of a 'back-seat'.

Another sub-theme (*'Staying involved with participants'*) set out that vaccine stakeholders volunteered the understanding that researchers should help participants with their medical needs because it represented relating respectfully to them in a non-using way and non-abandoning way. Another sub-theme set out that stakeholders perceived researchers as relating to people with real-life demands, and non-research commitments, whose lives could be significantly improved by the actions researchers take for them (*'benefitting and serving participants'*). These two sub-themes appear to capture something of the sentiment that it is wrong to merely use participants as a means to achieve the ends of researchers and it is right to treat them as ends in their own right (cf. Benatar, 2004). The subthemes also resonate somewhat (but not completely) with the factor of *'engagement'* theorized by ethical commentators to be significant when working out one's responsibilities to help address care needs (cf. Dickert & Wendler, 2009; Richardson & Belsky, 2004; Richardson, 2007; Richardson, 2012b; Richardson, 2012c). However, these stakeholders did not spontaneously volunteer the idea that the length or intensity of the researcher-participant relationship matters, as theorized by some commentators (cf. Richardson, 2012c) by rather that the relationship should be non-using and non-abandoning. Richardson and Belsky (2004) argued that even though the central purpose of trials is to generate knowledge, researchers should engage with participants as whole people not just as *'carriers of conditions or chemicals'* (p. 29). Richardson (2008) puts this quite starkly when he states that medical research enrolls human beings for experimentation and that ensuring their free informed consent to such experimentation alone does not adequately ensure that participants are treated as ends.

In a final view of the relationship (*Responding to/ caring for patients*) certain site-staff (mainly study clinicians) made sense of their care practices by anchoring them in the clinician-patient relationship, however, this was not the most frequently invoked characterization from interviewees. Very few stakeholders grounded researchers' ancillary-care responsibilities in the professional role-based responsibilities of clinicians (cf. Richardson, 2012c). This contrasts with the findings of Haire (2012) that the dominant account volunteered by her interviewees was that researchers had a doctor-like responsibility towards their participants and that researchers frequently invoked the clinician identity to justify ancillary-care practices for participants. This contrast may be partly informed by the fact that a relatively large portion of the interviewees in the Haire (2012) study were clinicians.

Various commentators have outlined the limitations of anchoring researcher–duties-to-participants in clinician-duties-to-patients, insofar as such accounts can be too easily ignored when researchers or site-staff encountering needs are not clinicians, or that such accounts (if not coherently limited) may lead to too much care being required of researchers (Richardson & Belsky, 2004; Richardson, 2012c). Miller et al. (1998) acknowledged that ‘physician-researchers’ may ‘gravitate towards their identity as a clinician’ or rely on their ‘self-understandings as healers’ to steer their actions in the research context (p. 1450) but they cautioned against using the physician-patient relationship as a model to work out investigator-participant care responsibilities. More specifically, they argued that the relationship between physician-patients and between investigator-participants differs crucially, that the central purpose of the researcher-participant interaction is not benefit to individuals as is the central purpose of the physician-patient relationship (Miller et al., 2008) that the basic goal of research is the acquisition of generally applicable scientific knowledge whereas the goal of care is personal therapy (Miller & Brody, 2003); that all research invariably includes some procedures with purely investigational purposes that would be precluded in personalized therapy (Miller et al., 1998; Litton & Miller, 2005) and that the activities of research may conflict with personalized care (Miller & Brody, 2003). Put simply, the physician-patient model calls for ‘undivided loyalty’ to the well-being of individual patients (Litton & Miller, 2005, p. 573). This finding suggests that (in the main) this reasoning is not frequently invoked by research stakeholders in the HIV vaccine trial field trying to understand the ancillary-care responsibilities of researchers.

These sub-themes suggest that stakeholders understand ancillary-care responsibilities as rooted in the researchers-participant relationship, where participants are construed variously as contributors, as ends-in-themselves, as worthy benefit-recipients, and (infrequently) as patients. The findings represent the personal, subjective understandings from vaccine stakeholders about why there are duties for researchers to help participants with their medical needs. These findings will not settle the matter of which ethical reasons are in fact the most rigorous or most convincing from a philosophical view-point. The findings will not convince (and not intended to) commentators committed to developing accounts that are not necessarily grounded in the researcher-participant relationship such as those grounded in

redressing global health disparities (cf. Benatar, 2000; Benatar & Singer, 2000; Benatar & Singer, 2010; Pratt et al., 2013; Shapiro & Benatar, 2005).

Stakeholder understandings likely depend on the time and place of data collection, for example, one could speculate that as HIV care components in low-resource settings have improved, the contrast with care in more resourced settings may appear less stark, and therefore arguments based on reducing-inequities might seem less appealing than a decade ago. No stakeholder in this study grounded researcher responsibilities to help participants with their medical needs in harm-based reasoning, more specifically they did not perceive that researchers should help participants address their HIV needs because the research increases the likelihood that participants will acquire HIV. It is possible that if this study was conducted now among increasing evidence that some vaccine-products increase the likelihood of HIV-acquisition if vaccinees are exposed to HIV (Gray et al., 2014) – even while a biologically plausible mechanism of action is disputed (Michael & Robb, 2014) - then stakeholders may have framed responsibilities in such ways, as found by Haire (2012) in her exploration of microbicide and other prevention trials.

## 5.2 RECONCILING

In terms of the second master theme (*'Reconciling'*) network and site-staff representatives across all sites implemented many responses to medical needs that formed no part of the scientific protocol they were pursuing but rather represented 'positive helping performances' or extra-scientific responses (Richardson, 2012c, p. 206) in addition to responses intended to promote science and safety. These findings showed that helping responses were implemented for medical conditions of varying degrees of scientific importance to the trial - from critical importance (HIV) to marginal importance (for example, hypertension). These findings show that site-staff and network representatives sampled here have embraced ancillary-care practices for a range of needs, and do not adopt a nil ancillary-care position (Richardson, 2012c). Site-staff made sense of many science-based steps as also helping participants in non-trivial ways and they made sense of many helping-based steps as also

-serving the science in non-trivial ways and they sometimes perceived the same response have having both effects.

These findings – both of practices and subjective understandings - suggest that network and site-staff representatives do not occupy a simplistic either-or position of 'pure scientist' versus 'personal physician' (Richardson & Belsky, 2004, p. 26/27) but are reaching for a more integrated position. They do not see themselves as (nor do they behave as) though they are serving the science exclusively nor as serving patient interests exclusively (Richardson & Belsky, 2004). These findings suggest that researchers do not adopt (either internally or in their actions) the position of 'blinkered scientist' or 'idealized physician' (Richardson, 2012c, p. 23) but rather are trying for an intermediate role (cf. Miller et al., 2008) or a middle ground (Dickert et al., 2007) that marries respect for the scientific endeavour with considerations of participant care.

The findings under one sub-theme (*'Taking steps to help'*) indicate that - across the needs of HIV, sexual and reproductive health, and even more general medical needs - network and site-staff implemented a range of responses that had very little to do with serving the interests of the research but rather had to do with helping participants to get their needs addressed (such as the network securing money from donors for an HIV treatment fund for HIV needs; or site-staff providing treatment for STIs onsite or site-staff referring participants for private care for general medical ailments while footing the bill). Findings that site-staff implement such helping responses correspond with the results of many prior explorations that document the myriad ancillary-care practices of researchers, including in microbicide trials (Heise et al., 2008; MacQueen & May, 2008; MacQueen et al., 2008; Ramjee et al., 2010); in HIV prevention trials including one vaccine site in South Africa (Ngongo et al., 2012); in malaria treatment trials (Pratt et al., 2013); and in public health intervention research (Taylor et al., 2011).

All of the afore-mentioned studies provide evidence that research initiatives of many kinds are including the provision of various forms of ancillary care, or implementing various extra-scientific responses for medical needs. These findings suggest at a minimum that vaccine

stakeholders do (and will) accept ethical guidance that requires them to implement some ancillary-care responses.

Three sub-themes set out that many site-staff perceived that when they implemented a response for a scientific reason it might have a real clinical benefit for participants (such as serial monitoring of CD4 counts and viral load leading to early referral for ART). In addition they saw that when they implemented an ancillary-care response it might have a real scientific benefit for the research, such as onsite treatment of ailments as leading to better reporting, and retention. They also perceived that some steps are underpinned by - or located in - both scientific and non-scientific reasons, such as tracking pregnancy outcomes because of fetal safety monitoring *and* because of a sense of involvement with the pregnant mother (*'understanding steps for science as also helping'*, *'understanding helping steps as soft science'* and *'understanding steps as for science and helping'*)

These stakeholders were not conflating responses implemented for a scientific purpose with responses implemented for a helping purpose or misunderstanding the primary purpose for taking a certain step (cf. Miller & Brody, 2000). This is worth noting because it has been argued that it is problematic when researchers view research from an exclusively therapeutic perspective (Litton, 2006; Miller et al., 1998). Miller et al. (1998) have asserted that it is most unhelpful when investigators adopt justifications for research, and for research procedures, that 'gloss over' the principal scientific motivations and that fail to recognise when procedures are intended primarily to generate scientific knowledge and not primarily to benefit participants (p. 1450).

The findings here do not suggest that investigators have fallen prey to the 'seduction' of the 'therapeutic misconception' (Miller et al., 1998, p. 1451). They did not believe that procedures intended for scientific purposes are being implemented primarily to benefit participants (Appelbaum, Loren, Roth, Lidz, Benson & Winslade, 1987; Miller et al., 1998) but rather they recognised spin-off clinical benefits for participants from research procedures. They seemed to acknowledge that therapeutic benefits *may* derive from research procedures as part of the context of research but not as the primary purpose of the research (Miller et al., 1998).

This study also showed that site-staff perceived that helping responses can serve to improve scientific outcomes. It is as though these stakeholders augment their justifications for implementing ancillary-care responses on grounds of positive, welfare-promoting reasoning as set out in the first master theme with this additional consideration (which may of course be palatable to research sponsors whose mission is research). Previous empirical explorations have also documented the perspective that ancillary care can inadvertently strengthen recruitment or retention (cf. Heise et al., 2008; Philpott et al., 2010) – which has been referred to some commentators as a soft science justification for ancillary care (Richardson, 2012c).

These meanings attributed by interviewees to their conduct (as well as their actual conduct) indicate efforts to integrate research-related responsibilities with more positive, helping-based responsibilities, and to reduce the tensions between the two. However, this data shows that tensions between science and welfare-promotion remain across HIV, contraception and pregnancy needs (as set out under *'Understanding some steps for science as not helping'*). More specifically, site-staff viewed some scientific responses (such as inviting participants with HIV onto disease-monitoring protocols, requiring contraceptive compliance for the duration of the study and counselling participants terminate pregnancies) as potentially clashing with helping participants with their important health needs.

These findings resonate with the observation that it is difficult to eliminate potentially competing loyalties between generating important knowledge and promoting participant welfare, and this tension needs careful management (Miller et al., 1998). Current HIV prevention specific ethical guidance does not currently directly speak to the issue that scientific procedures may conflict with perceived best care for participants, even while such conflicts are explicitly recognised for the provision of prevention modalities to participants. More specifically UNAIDS/WHO (2007; 2012) allows that site-staff may experience conflict between reducing the risk of HIV acquisition (on the one hand) and needing sufficient HIV infections to accrue on efficacy trials (on the other hand). Ethical guidelines may wish to incorporate some text that alerts readers to the potential conflict between serving the science of HIV vaccine trials and serving the interests of participants, which is a point revisited in the next chapter. It may help for each site to have space for careful reflection on this issue,

as part of an internal ancillary-care review, which is a point revisited under recommendations for practice in the next chapter.

### 5.3 PRIVILEGING

Under this master theme (*'Privileging'*) stakeholder conflicts are discussed regarding the prioritizing of participants over non-participants for the implementation of helping-based responses, and related concerns and complexities. The reader will remember that, under the first master theme, many vaccine stakeholders perceived researchers' ancillary-care responsibilities as rooted in the researcher-participant relationship, and set out various conceptualisations of that relationship that underscored how participants might have a particular 'moral pull' on researchers that other equally needy citizens might not have (cf. Metz, 2010, p. 55). Despite perceiving relationship-based reasons for ancillary care that give researchers reasons to give priority to their participants instead of steering their help to non-participants (cf. Richardson, 2012c) site-staff and other stakeholders experience some conflict over how much privileging is ethically acceptable and how the consequences of such privileging should be managed.

Certain stakeholders (especially site-staff) had within-person ambivalence about how much special treatment participants deserve in relation to citizens (*'questioning special treatment for participants'*). They endorsed that some special treatment was allowable – if not essential – and was in fact happening (there is more on this point later) but they questioned how different the care approach for participants should be from the approach that citizens would experience. They did not know within themselves how much special treatment was acceptable.

Certain stakeholders (network representatives, site-staff and REC representatives) endorsed that some special treatment was acceptable for participants (that is, that researchers should take steps for participants that they do not necessarily take for non-participants) however they did not agree between themselves on precisely what that response should be (*'endorsing special treatment but not agreeing on response'*). Even when they anchored researchers' need

to respond in the contributions that participants make, they did not always share an identical understanding of what response was owed.

These findings resonate with observations in the literature that, even when obligations are viewed as rooted in reciprocity, questions will still remain about the extent of the response (Millum, 2010). More specifically, Millum (2010) argued that the return, or reciprocal benefit, or what participants are owed (from those who have invited participation) should be *appropriate* to the contribution made by participants including costs incurred and extent of the benefit provided by the research. Merrit and Grady (2006) argued that the return from those who stand to benefit should be *proportionate* to the sacrifice made by participants. Millum (2010) noted if the participants incur substantial costs or if the benefits generated by the research are great enough, then sponsor-investigators may have responsibilities to take demanding steps to address medical needs.

These findings suggest that stakeholders agree that participants should get some 'special care' (Richardson, 2012, p. 122) but there is some within-person and between-person conflict about precisely how much special care they should receive – what is a proportional response? This finding shows that many stakeholders do not support 'interpersonal equality' between participants and non-participants (cf. Merrit, 2011, p. 330) but they still have some concerns about how much deviation from treatment-for-citizens is acceptable – how much better should the approach be for participants versus others? That is, these findings indicate that these stakeholders do not necessarily have discomfort about individual attention *per se* being paid to participants (Lo et al., 2007) but they have concerns about the degree of attention to be paid them. These findings suggest that stakeholders do have concerns about how people inside a trial and people outside a trial based in the local community are treated (Haire, Folayan, Hankins, Sugarman, McCormack & Warren, 2013). That is, stakeholders do have concerns about prioritizing the interests of participants in relation to non-participants (cf. Merritt, 2011). They do not appear to reject it outright, but rather they question *how much* special treatment is acceptable, or they do not share the same understanding of *how much* special treatment is acceptable.

These findings suggests that ancillary-care guidance will not need to convince stakeholders about *why* it would be acceptable to treat participants partially (remember they invoked reasons under the first theme that would support this) but it should try to provide guidance on *how much* deviation from how everyone else is treated is acceptable (cf. Brownsword, 2007) or how much deviation from impartial treatment is allowable (cf. Merritt, 2011). This suggests that it would be especially helpful for vaccine stakeholders if guidance tries to help with establishing the 'dosage' of differential treatment. Guidance may need to better spell out the need to consider whether responses are proportional to the contribution being made by participants; or whether the benefit is appropriately sized. This point is revisited in the next chapter.

This complexity (within-person and between-person disagreement about the proportional response) suggests that a possible solution would be on-going reflection and consensus-building about what responses would constitute appropriate or proportionate responses to participants' contributions. It is possible that the lack of agreement seen in this study about the precise response owed to participants (captured here under this third master theme) is linked to differing notions of what is contributed by participants (captured under the first master theme). This point is re-visited under recommendations for practices.

The findings also showed that site-staff actually recognized that participants *are* in fact somewhat privileged in relation to citizens (they understand participants as receiving a reciprocal return or getting a benefit that citizens do not) (*'recognizing some privileging of participants over citizens'*). But site-staff appeared ambivalent about declaring these advantages in protocols and consent forms. Medical benefits reportedly associated with research procedures themselves (for example, serial monitoring that allows early referral for ART) and medical benefits reportedly associated with care strategies for identified conditions (for example, less time-wasting if STIs are treated onsite) were not stated in protocols or consent forms as potential benefits. That is, despite understanding that some advantages accrue to participant, such advantages were not readily declared in these written documents (Slack, 2014) (*'not declaring benefits in ICFs/ protocols'*). It seems that not declaring benefits is not because researchers are lazy, or distracted but may be because they are uncertain about

proportional returns or appropriately sized benefits for participants (relative to non-participants). This is an issue worth further exploration as recommended in next chapter.

Site-staff and network representatives were also concerned that if participants were given too much special treatment then citizens might want to become participants too uncritically (*'worrying about the consequences of special treatment'*). These stakeholders were concerned about the consequences of broadcasting special treatment, namely, that informing participants about the return or the benefit might make citizens make poor decisions about being in trials. Here concerns were that people would be inappropriately induced (or even 'coerced') into trial participation if they knew at the outset that they would be getting better care than non-participants, or if they knew how much better that care would be.

This concern resonates with theoretical debates about the impact of offers (and even threats) on voluntariness of participation (Appelbaum, Lidz & Klitzman, 2009) and consensus that participants should make decisions free from substantial controlling influences (Grady, 2002) or free from external, intentional and illegitimate influences (Appelbaum et al, 2009). The latter includes so-called undue inducements - defined as an excessive offer that distorts the processing of risks or causes the devaluation of risks (CIOMS, 2002; Emanuel, 2004; Slack et al., 2005). Concerns that ancillary care might lead participants to discount risks have long been registered (Dawson, Klingman & Matarazzo, 2014). Rebuttals include that undue inducement is minimized where offers are modest (Emanuel, 2004), where consent strategies are implemented to assist participants to carefully process risks (Slack et al., 2005) and where research risks are reduced to an acceptable level by competent ethical review (Emanuel, 2004). Also, efforts should be made to ensure that offers are well reasoned or well justified. Ethical commentators have also argued that offers of improved medical care can never constitute coercion because offers are not direct threats that will leave participants worse off than they were before the interaction with researchers (Emanuel, Currie & Hermans, 2005; Hawkins & Emanuel, 2005). Ethical guidelines also take this issue head-on by stating that undue inducement concerns are often inappropriate (cf. UNAIDS/WHO, 2007; 2012).

Despite this scholarship and guidance, this data suggests that impact-on-decision-making is a lingering ancillary-care concern for stakeholders. These findings suggest that ancillary-care

guidance should address the issue of undue inducement and coercion in some detail, with more explication of strategies to offset such concerns, including consent processes to ensure good decision-making in the face of ancillary-care benefits.

It is worth noting that no vaccine stakeholder here spontaneously raised the concern that upfront disclosure of potential trial-associated benefits (either benefits from research procedures or benefits associated with ancillary care) would cause a 'therapeutic misconception' in participants (cf. Appelbaum et al., 1987). Concerns about the therapeutic misconception are that patient-participants may misconceive the intentions of researchers and research (and research procedures) as therapeutic (Litton & Miller, 2005) or may have the false belief that the study as a whole and specific study procedures in particular 'are designed to provide personal medical benefit' (Miller et al., 2008, p. 271) or have an unreasonable appraisal of the medical benefits associated with participation due to misperception of the nature of research (Richardson, 2012c). It is possible that research stakeholders do in fact have some misgivings about disclosures of benefits grounded in worries about the therapeutic misconception but these were never spontaneously volunteered, and this should be explored in further research (a point returned to later). Regardless, it would appear that concerns about the therapeutic misconception could be offset by careful consent strategies (cf. HPTN, 2009) or by clear communication about the distinctions between research versus care components (Presidential Commission, 2013) and therefore such concerns would not provide good grounds to strip out all benefits associated with implementing ancillary-care responses.

It is important for ancillary-care guidance to address both concerns (both about how much advantaging is acceptable and about the consequences of advantaging) because until this is achieved stakeholders are likely to resist instructions to include fuller descriptions of benefits in written materials. The quick-fix solution would be to instruct site-staff to do better written disclosure about benefits, but the underlying worries would remain unaddressed. Not detailing potential benefits does have consequences. When anticipated benefits are not declared in *protocols* then reviewers cannot judge their appropriateness, which is considered to be a key task in ethical review (UNAIDS/WHO, 2007; 2012). Furthermore when anticipated benefits are not declared in *consent-related material* then it may undermine participants'

comprehension of the personal implications of their participation (Lindegger & Richter, 2000; Lindegger et al., 2006) or the 'research 'impact', including 'additional potential for clinical benefit' (Wendler & Grady, 2008, p. 207). Participants' understanding – including of potential benefits - should be facilitated by providing them with appropriate written material (Woodsong & Abdool Karim, 2005) and by regular verbal discussions with site-staff (cf. Flory & Emanuel, 2004).

Some commentators have asserted that far more attention should be paid to considering whether potential benefits to participants 'can reasonably be claimed' and if so how they should be described in the consent form and process (King, 2000, p. 332). King (2000) argued that claims of potential benefit should be supported by actual evidence and then consent material should contain carefully crafted, detailed statements about potential benefits. The findings here (that consent materials say little about the benefits that are believed to accrue to participants from research procedures or ancillary-care responses) suggest that written materials are relatively silent on what King (2000) terms collateral benefits to participants arising from design features such as physical examinations, monitoring, tests but also including so-called free care or other extras. These collateral benefits are considered distinct from direct benefit to participants arising from the experimental intervention and distinct from aspirational benefit to future persons and society arising from the research results. The findings here suggest that relative silence on collateral benefits may be linked to concerns about the impact of inducements on participants' decision-making. This is despite recognition in the literature that participants' motivations for research may well stem from the hope of collateral benefits, and not only from the desire for aspirational benefit to society (altruism) or the chance of benefit from the experimental intervention (King, 2000).

The findings here do indicate that stakeholders had two distinct sets of concerns about privileging participants in relation to citizens – they have concerns about how much to do it, and they have concerns about declaring it. These imply different solutions. The former problem needs better guidance for *how much* privileging is acceptable (and needs to be convincing about how much of a return or benefit participants deserve in relation to citizens or the most appropriately dosed response) and the latter problem needs better guidance about why privileging might not necessarily undermine decision-making. Taken together

(and a point I will return to in recommendations for ethical guidance), these findings show that stakeholders need some help establishing the appropriate degree of benefit for participants related to ancillary care. Additional research could explore the discomfort around benefits more fully (see recommendations for future research).

Site-staff implemented some responses to assist volunteers being screened for trials with their medical needs, and to assist general community members with their medical needs, perhaps to offset some discomfort about privileging participants. Previous empirical explorations also found that site-staff undertook various practices to help non-participants get their medical needs addressed (Heise et al., 2008; MacQueen & May, 2008). Practices found in this study tended to exceed what ethical guidelines require for volunteers and underscore that ethical guidelines are a little 'thin' on actual direction for volunteers (cf. Slack, 2014). Ethical models such as partial entrustment and whole person would allow that less is owed to volunteers screened out than is owed to participants actually enrolled (because there would be less indebtedness for risk and burdens, and less engagement, in brief screening protocols than in actual HIV vaccine trials) and they would allow that more is owed to volunteers enrolled in screening protocols than citizens enrolled in no protocols – which is an approach consistent with the actual conduct of researchers in this study.

Site-staff also implemented various strategies to address participants' needs that indicated that participants *at some sites* were likely privileged over participants at other sites (for example, some sites offered onsite treatment for STIs or other ailments, preventing timewasting, whereas other sites did not; and one site referred participants to private-sector practitioners for some general ailments whereas no other site did so; and sites referred to off-site facilities of varying quality). These stakeholders expressed little conflict about between-participant differences and in fact variable strategies for meeting participants' needs were endorsed if not downright valued.

Prior explorations have identified that sites address needs via a combination of direct or indirect (referral) strategies (Heise et al., 2008; MacQueen et al., 2008). As set out in Slack (2014), some commentators have called for a standard 'approach' to care services (Ngongo et al., 2012, p.2). Others have asserted that there is no single solution to addressing participants'

care needs (MacQueen et al., 2008) even while voicing concerns about comparability of care across sites (MacQueen et al., 2004). While sites can *aspire* to similar strategies (for example, onsite provision of treatment for STIs with associated advantages) it may be constraining to *mandate* this because it disregards the unique context and situation of different sites. Instead, site-staff should be alert to quality problems with all strategies, as part of an ongoing commitment to reflect regularly on their ancillary-care approach, which is a point made in recommendations for practices. Calls for 'standardization' of care approaches (cf. Ngongo et al., 2010) need critical engagement, because findings here show that various strategies and referral sites are utilized (that is, the 'seeing-to-it' of participants needs differs across sites within the same country) with embedded quality differences for participants across sites, but that flexibility is endorsed and valued. These findings suggest that guidance on ancillary care should address whether (or how much) inter-site differences are acceptable. That is, comprehensive ancillary-care guidance will need to offer good reasons for why it is acceptable to depart from a more impartial, uniform approach to participants across all sites, and treat participants at different sites differently. Some commentators have already noted that more thought should be given to whether the needs of participants in a single study but across different sites should be treated differently (Richardson, 2012c) and this data underscores this observation, especially because site-staff appear to value the freedom to implement different responses at different sites, based on site characteristics and surrounding context.

Current ethical guidelines offer very little direction on across-site, within-country differences. Previous guidelines asserted that trial sponsors should ensure that 'core elements of the package' of care are consistent (UNAIDS/ AVAC, 2007, p. 29). This appears to miss the issue here – that participants access the same elements of care, but the strategy or the referral-site characteristics introduces modest but non-trivial quality differences between participants at various sites (Slack, 2014). More explicit direction on this issue is recommended. Current ethical guidelines speak to differences between countries, tending to argue that researchers reach for equivalent standards across country settings (UNAIDS/WHO, 2007; 2012). One might infer that the same is called for across 'micro' settings such as sites, however, an explicit stance on the issue would be helpful. This is a point returned to in the final chapter under recommendations for ethical guidance.

As set out under the results, no stakeholder here appeared concerned that special treatment of participants might set citizens back (by for example queue-jumping), but rather they appeared concerned that citizens may be excluded from benefits that participants get. Furthermore, steps taken for participants would not appear to demonstrably *set non-participants back* (Merritt, 2011). For example, representatives from all sites described assisted-referral steps for HIV (such as checking participants' referral preferences, securing participants' permission to share medical information about HIV, developing plans for referral) and some sites reported additional practices (such as booking appointments, alerting referral sites, accompanying participants, and intervening at referral sites). There is little reason to believe that such practices would take much away from non-participants. Because participants were serially monitored and referred promptly for ART (with their evaluation results) such monitoring does not have to be provided by public-sector facilities which potentially frees up finite resources to be used for non-participants (cf. MacQueen et al., 2006; 2008). This suggests that steps for participants do not divert or displace resources away from non-participants (Richardson, 2012c) leaving non-participants worse off than they were before but rather that the interests of citizens are not advanced as much as participants.

These findings do not suggest that vaccine stakeholders need clearer reasons for why researchers should prioritize participants over non-participants (the reader will remember most stakeholders invoke reasons that would support this view - such as reciprocating for participants' contributions, staying involved with participants, conferring benefits on participants). However these findings do suggest that stakeholders need help with the proportionality of responses, and extent of benefits, as well as the consequences of privileging for decision-making and therefore that ethical guidance should assist with these concerns.

#### 5.4 **LINE-DRAWING**

In terms of the fourth master theme (*'Line-drawing'*), and with regard to addressing needs, site-staff and network representatives used several ideas to help them work out what responses should be implemented – namely, the relationship of the need to the overall

research mission (when *needs* were viewed as strongly related to the research or the research question then more demanding responses were viewed as more acceptable) and the costliness of the response in terms of the impact on the overall research mission (research-undermining *responses* were viewed as unreasonable). Despite using these ideas to set limits on responses, there were several occasions where they questioned whether their own responses were adequate, or if they should be doing more. Line-drawing was also undertaken with regard to other ancillary-care activities, such as engaging the community for ancillary care. REC representatives also drew the line around their review responses.

At its most basic, this master theme shows that stakeholders agree that there are limits to ancillary-care responsibilities, and that stakeholders are not 'one-sidedly pro-participant' in their ancillary-care views (Richardson, 2012c, p. 222). Ancillary-care responsibilities are not viewed as unbounded or unlimited. Many ethical commentators writing about ancillary care recognise there are limits on researchers' ancillary-care obligations (Merritt, 2011) and this data – at a minimum – shows that stakeholders agree there are limits, and are trying to set such limits in a non-arbitrary way.

These findings ('*understanding some needs as in focus*' and '*understanding needs in focus as deserving more demanding responses*') suggest that stakeholders do consider the linkage of the need to the research question to be relevant. They appear to recognise that needs are of varying degrees of relevance or significance to the actual trial, and by implication of varying degrees of significance for researchers' attention. That is, stakeholders in this study seemed to agree with the idea that as researchers encounter conditions that are closer to or more connected to the research question, the more important it is that researchers take steps to address the need even if responses are demanding. They seemed to support the idea that needs centrally connected to the research question should be somewhat privileged for more demanding responses – but they were not advocating that other needs be ignored, or that no ancillary-care responses be implemented for them. This suggests that stakeholders do embrace concepts that resonate with the 'scope' factor theorized to be of importance in the partial entrustment account (cf. Richardson, 2012c). Findings about site-staff practices show that other needs are not neglected and researchers do implement helping-based responses for these other needs or for non-endpoint conditions (as set out in '*Reconciling*').

Despite some ethics commentators questioning the relevance of the connectedness of participants' need to the research question when making ancillary-care determinations (Dicker & Wendler, 2009) these findings suggest that these stakeholders see such 'connectedness' as somewhat relevant to their ancillary-care considerations and they place some importance on the connection of the need to the study question (cf. Dickert et al., 2007).

There is little data in this study that can address whether stakeholders support the view that it is needs identified by study procedures (after permission-giving and privacy-waiving by participants) – so called 'entrusted' needs or needs falling in scope - that are the most eligible for the special duties of researchers as opposed to needs identified by other non-research methods (a key point for the partial entrustment account). Study questions were not specific enough to untangle whether stakeholders see as significant *how researchers come to know* about needs - which should be explored in additional research. Also, stakeholders did not spontaneously volunteer any observations that suggest they see special responsibilities of researchers as arising because of the permission-giving and privacy waiving in the consent process (a key feature of the partial entrustment account) (cf. Richardson, 2012c).

In the first master-theme, stakeholders perceived that the researcher-participant relationship counts when making ancillary-care determinations but those subthemes did not necessarily support the view that the relationship is started by permission-giving in the consent process as promoted by the partial entrustment account (cf. Richardson, 2012c). Put more simply, there is little data in this study that can shed light on whether stakeholders place great importance on the connectedness of the need to the *study procedures* when deciding about ancillary-care (cf. Dickert et al., 2007). One could speculate that the study procedures implemented in HIV vaccine trials (such as full medical history-taking; full physical examinations; as well as numerous laboratory tests) lead to such a broad range of needs being uncovered by so-called study procedures that few conditions would remain to be identified casually! Regardless, this distinction should be explored more fully in further empirical research, which is recommended in the final chapter.

Site-staff and network representatives held their central mission in high esteem (*'invoking primary mission'*). Site-staff and network representatives characterized some responses as potentially undermining the overall research mission which was seen as valuable and non-trivial. They saw that implementing overly-costly responses was an important way of setting limits on their particular responses (*'invoking costliness of certain response on primary research mission'*). That is, they used the idea of the 'demandingness' of a certain response, in terms of its impact on their core mandate, when considering the steps they should take. This data suggests that these stakeholders understand their research mission as benefitting a collective and this can represent a sound rationale to resist unbounded ancillary-care responsibilities towards participants (Richardson, 2012c) or unlimited care responses (Dickert et al., 2007).

These findings suggest that when researchers and network representatives consider ancillary-care responses they implicitly juxtapose two main parties, namely here-and-now participants versus prospective future beneficiaries of the trial (cf. Merritt, 2011). These findings suggest that researchers and network representatives use the interests of future beneficiaries of the research to establish limits on their obligations to current participants, and consider the moral importance of addressing a huge public-health problem as a way of setting limits on responsibilities to participants before them (cf. Merritt, 2011). They attempt to balance research objectives (which are long-term and critical) with the needs of individual participants (which are immediate and serious) (cf. Richardson, 2012c).

At a minimum, these findings explicate the countervailing reasons offered by vaccine stakeholders or reasons against unlimited ancillary-care responses (Merritt, 2011; Richardson, 2007). Findings suggest that stakeholders' lay ethical notions or intuitions correspond somewhat with factors in the partial entrustment account and whole person accounts of ancillary care referred to as costs - where it is noted that demandingness of a response may be a valid reason not to implement it (Dickert & Wendler, 2009; Richardson & Belsky, 2004). Stakeholder perceptions correspond with the costs of scientific-impact and budget-impact and staff-impact as theorized by Richardson (2007, 2008, 2012c) yet these findings suggest that researchers foresee an additional cost – namely shouldering the legal demands of being responsible for participants' care. This issue should be more fully explored, which is a point returned to under recommendations for future research. Of course, this finding does not in

and of itself theoretically vindicate this aspect of the partial entrustment or whole person accounts, but suggests that stakeholders in the field perceive these factors to be relevant.

Many ancillary-care commentators allude to the so-called costliness of ancillary-care responses (Brownsword, 2007; Merritt, 2011; Richardson, 2007). They assert that ancillary-care responses or duties of 'ancillary assistance' should not be 'overly demanding in relation to researchers' essential interests' (Brownsword, 2007, p. 5) or be so demanding that the research is scuppered (Merritt, 2011). Findings about the actual practices implemented by site-staff and network representatives suggest that some responses exceed the limit-setting threshold inherent in rescue-based accounts - namely that the so-called rescuers should not be 'inconvenienced' - because many responses reported here appear to involve considerable inconvenience (such as setting up HIV treatment fund; engaging stakeholders in partnerships for care; and hiring dedicated staff to such ends) such that these responses would not qualify as simple or cheap interventions that involve easy fixes or slight sacrifices (Merritt, 2011). This suggests that stakeholders might embrace accounts of ancillary care that require them to move beyond easy fixes to more demanding responses – and both partial entrustment and whole person accounts would fit here (as might others). This does not mean that rescue-based accounts could not cover some of the responses identified here, especially low-cost responses for participants, or even responses implemented for general citizens (such as screening for glucose levels).

This sub-theme should also be read with sub-themes under '*Privileging*' which suggests that it is not merely whether a response is overly costly that is of concern to stakeholders but also (more implicitly) whether it is proportional to participants' contributions. Read together, it is as though these stakeholders are seeing an acceptable ancillary-care response as one that it both *demanding-but-not excessive* as well as *proportional to contributions*.

Despite using several important notions to set limits on their responsibilities, or to draw the line around their responsibilities, site-staff and network representatives still experienced nagging concerns (but not too acute or overwhelming) about whether their responses were reasonable or whether a case could be made for them doing more. The concrete situations raised by these stakeholders in relation to participants' needs included: Should early ART-

initiation be implemented for participants? Should a third-line ART regimen be provided for participants acquiring resistance to first-line or second-line regimens even if not routinely available? Should participants in high-income settings with threatened access to ARVs be enabled to access ARVs through the network's treatment fund? Should volunteers screened-out of trials because they are HIV-infected be provided with better monitoring in the form of CD4 counts and viral load measures? Should participants be provided with diagnostic screening for STIs as opposed to syndromic management? Should site-staff procure IUDs for contraception and hire/ train staff to insert them for participants? The sub-theme ('*questioning approach/ responses*') indicates that comprehensive ancillary-care guidance should be able to help stakeholders work out whether their responses are adequate, or whether they should be implementing better, different responses.

Ethical models of ancillary care might help stakeholders address the concrete questions identified empirically in this study by providing them with conceptual tools to navigate concrete situations. Such accounts often do not suggest an actual standard that researchers should strive for (cf. Participants, 2008) but rather suggest a threshold of costliness for planned responses (Merritt, 2011). Rescue-based models would posit that researchers implement responses that are not-inconveniencing to the rescuer, whereas partial-entrustment or whole-person models would posit that researchers implement responses that are demanding but not research-scuppering. Because the responses implicated in the above questions involve costs exceeding mere inconvenience, rescue-based approaches are unlikely to provide helpful guidance, and partial entrustment or whole person accounts are likely to be more useful. This is because the latter accounts set out that there may be good reasons for researcher to implement responses that are costly enough to exceed slight sacrifice or inconvenience.

On the latter accounts researchers should implement an ancillary-care response unless the response reaches the threshold of being excessively or inordinately costly to the point of overwhelming the scientific project (Merritt, 2011), undercutting good science (Dickert & Wendler, 2009), or frustrating scientific goals (Richardson, 2007). For example, those accounts of ancillary-care would encourage stakeholders to ask whether the specific response of *ensuring access to early post-infection initiation of ARVs* would reach such a threshold of

costliness? Janes, Gilbert, Buchbinder, Kublin, Sobieszczyk and Hammer (2013) noted that early post-infection initiation of ART means that fewer vaccine trial participants will have post-infection endpoints measures (beyond the acute phase) making it more difficult to assess the impact of the vaccine on post-infection disease course. It is possible that some participants would not choose early treatment even if this is offered and it is also possible that early treatment would still allow many post-infection endpoints to be assessed, for example, even if ART is offered at a CD4 count of 500 it may take a newly infected person about four to five years to reach such a CD4 count (Glenda Gray, personal communication, 29 January 2014). The 'costs' are not likely to reach the threshold of impeding the scientific goals and would not represent good enough countervailing reasons not to implement such a response for willing participants. In a similar vein, the models would have stakeholders ask if the specific response of *providing third-line ARVs* (if needed) to participants would reach the threshold of excessively costly? If this assessment showed that a modest number of participants might acquire resistant HIV, and that the financial costs of procuring third-line ARVs would be low in relation to the overall budget, then threshold of excessively costly would not be met for this specific ancillary-care response, and this response should be implemented for participants. Also, these models would have stakeholders ask if participants in high-income settings in which access to ARVs was threatened should be allowed access to the network's treatment fund, and if this assessment showed that few participants in such settings are likely to require such coverage, and that the financial burden is likely to be low in relation to the overall budget, then this response should be implemented. It is most likely that both assessments would show that these specific responses should be implemented.

These models would have stakeholders consider the uncompensated risk and burden assumed by volunteers who take part in screening procedures (comprising medical history, physical examination, assessment of current medications, HIV testing, pregnancy testing, assessment of sexual risk behaviour, and assessment of their willingness to use reliable contraception) and presumably these would constitute the potential for anxiety regarding test results, and embarrassment from talking about risky behaviours, as well as time spent at the site. The length and intensity of engagement with volunteers would have to be explicitly considered, even while it is generally considered minimal for screening procedures (Richardson, 2007). The additional costs imposed by conducting and communicating CD4 and viral load assessments for those volunteers identified as HIV-infected would have to be

considered. These models would provide a framework for working out if this particular response presented additional bearable costs over and above the costs of other responses also being implemented for volunteers (such as onsite treatment of various ailments in many cases). Presumably, but more implicitly, these models would provide a framework for working out if implementing this particular response in addition to other responses also being implemented for volunteers would represent a more proportional response to volunteers' overall contributions. This point about proportionality as a concept for more elaboration is made again in the next chapter.

Ethical guidelines do not explicitly address the concrete situations raised by these interviewees as set out above but they do recommend standards to strive for – particularly for HIV, and particularly for participants. UNAIDS/WHO (2007) recommends that investigators should integrate with national treatment plans and local systems, and modify treatment plans in line with updated national guidelines (UNAIDS/AVAC, 2011). This implies that researchers should ensure that participants with HIV receive HIV treatment established by national norms in the host country. The same guidance document recommends that participants in 'high, low and middle-income countries' receive equivalent treatment (UNAIDS/WHO, 2012, p. 65). This implies that researchers should ensure for participants with HIV access to the HIV treatment that is normative in high-income countries. Therefore, the UNAIDS/WHO (2007; 2012) guidelines are not silent about so-called 'line-drawing' for HIV (that is, the issue is addressed) but the readers may be left with some questions about which standard should prevail – it sufficient if participants' HIV care is indexed to national norms when these norms include access to an ART regimen, or should participants' HIV care be indexed to international norms in all ways?

If the former standard is endorsed, it follows that researchers should take steps to integrate participants into national treatment programs, where they will receive ARVs endorsed by national treatment guidelines, as well as initiate ART following national treatment guidelines. If the latter standard is endorsed, it follows researchers should take steps to reach an international standard, by for example, procuring third line ARVs for resistance for participants if these are available in high-income settings even if these are not available in the public-sector, or by initiating participants on ART earlier if international treatment guidelines

advocate for this even when domestic treatment guidelines do not adopt this approach. Of course, it is entirely possible that the UNAIDS/WHO (2007; 2012) guidelines intend the national standard to represent the 'floor' or minimum that researchers should achieve, and the international standard to represent the 'ceiling' for which researchers should strive; but then this intention should be stated more explicitly. Their guidance might be strengthened if recommendations were added for researchers to do as much as they can to help participants address their medical needs without exceeding a certain threshold of costliness – the approach adopted in various recent accounts of ancillary care, as well as in the HPTN (2009) guidelines. These are points made again under recommendations for ethical guidelines.

Findings from this master theme should be read with those from the first master theme, which suggests that ancillary-care guidance is likely to be viewed as relevant if it helps set limits on ancillary-care responsibilities by referring not only to notions of 'costliness' but also to notions of 'proportionality' because both notions appear to be significant to vaccine stakeholders. Partial entrustment or whole person accounts do include such notions, but both accounts could do more to demonstrate that the concept of 'gratitude' (or preferably 'indebtedness') has a place in working out how far one should go to help *as well as* the concept of 'costliness'. Put more concretely, instead of asking stakeholders to consider questions such as 'will the response be excessively costly by for example impacting on the science?' or 'will the response be excessively costly by for example monopolizing staff time?', an additional question should be asked namely 'will the response demand a cost or sacrifice that is disproportionate to what has been contributed?'

## 5.5 PARTNERING

In terms of the final master theme ('*Partnering*'), site-staff were engaged in relationships with multiple stakeholders in ways that were orientated towards securing care for participants. These relationships were viewed as partnerships where the distinctive contribution of various partners was recognised, as well as their capacity and commitment. At a minimum, this data shows the practices of various actors quite concretely - as called for by Richardson (2012c). This indicates that these stakeholders understand and endorse that ancillary-care responsibilities should be allocated to various agents that are in a position to help (Meritt,

2011). This suggests that stakeholders do not expect researchers to shoulder the entire burden of ancillary care for participants. This data also shows that various agents share out ancillary-care practices and responses amongst themselves.

Partnerships were characterised as involving some tension, where the adequacy of the partners' care response was questioned. Commentators have pointed to the 'evolving and sometimes tense dynamics of HIV prevention partnerships' (UNAIDS, 2006, w1) even while establishing long-term partnerships to achieve care has long been recommended (IAVI, 2012). This study explicates some of the underlying dynamics of these partnerships. Findings show that in some instances stakeholders *questioned if their partners were doing enough* to help improve care for participants or if partners could be implementing different (better) ancillary-care responses. It is as though stakeholders recognised that partners must draw a line but they questioned where the partner has drawn the line. This data suggests that useful guidance about ancillary care should also set out the responses (and limits) of researchers attempting to engage non-researchers to ensure ancillary care – a point returned to in the final chapter.

#### 5.5.1 SITE-STAFF AND PARTICIPANT INTERACTIONS

This study found that a small proportion of participants at every site that were found to be HIV-infected reportedly did not access HIV care, despite measures to encourage them to do so - a finding that dovetails with results from previous explorations of ancillary care (Heise et al., 2008; Ramjee et al., 2010). Site-staff characterized participants as holding considerable power regarding whether offers of ancillary-care would actually be taken up and fulfilling the observation that in a small number of cases one cannot 'assume the relevant care is wanted by those who need it' (Richardson, 2012c, p. 92). Richardson (2012c) also noted that 'ancillary care ought not to be pressed on an unwilling recipient' (p. 94). In the next chapter the recommendation is made that participants' viewpoints on this issue should be explored.

#### 5.5.2 SITE-STAFF AND SERVICE-PROVIDER INTERACTIONS

The results showed a range of practices that site-staff engaged in with local public-sector service-providers, including but not limited to assessing referral-site functions and

capabilities, highlighting the site's purpose and functions; reaching agreements about sharing participant information; sharing medical information about participants; soliciting feedback from referral sites; providing training; collaborating on health-related events; involving such representatives in CABs; and engaging them to procure hormonal contraception or treatment for STIs for onsite dispensing. Often these activities were undertaken by specially trained staff or staff specifically employed to undertake outreach-type functions. These practices or similar ones have been reported in many other empirical explorations (Clouse et al., 2010; Heise et al., 2008; MacQueen et al., 2008; Ngongo et al., 2012; Ramjee et al., 2010). It would appear that site-staff perceived these ongoing referral-based relationships as requiring more than simple, undemanding, short-term steps.

The practices volunteered in this study suggests that researchers recognised the importance of understanding the assets and constraints of public-sector facilities, of building relationships with such resources including clarifying mutual expectations (MacQueen & May, 2008) and addressing false assumptions (MacQueen et al., 2008). It also suggests that site-staff recognised the advantages of referral strategies – namely linking participants to local care (MacQueen & May, 2008) enhancing the likelihood of continuous care (MacQueen et al, 2006). MacQueen et al (2008) noted that participants' health needs (especially for chronic conditions) 'extend well beyond the life of a clinical trial – potentially decades beyond' (p6). As noted in Slack (2014) these efforts to engage referral partners accords with the recommendations of MacQueen et al (2008) to design trials 'to function as integral components of public health systems' rather than 'stand-alone endeavours' (p. 15). Researchers recognized the critical importance of strong linkage from testing to care, especially for participants with HIV (Hallet & Eaton, 2013).

Site-staff in this study sometimes questioned the adequacy of care-partners' responses to participants' needs, more specifically, the long wait times and poor counselling at public-sector referral sites for STIs and contraceptive needs, as well as slow implementation of initiation criteria for ART at select referral sites. Hyder and Dawson (2005) noted that system inefficiencies often determine the care that is actually meted out in particular locales. MacQueen et al (2008) noted that participants' unmet needs often reflect failure of other stakeholders to implement their responsibilities, and in such instances, the best response for

researchers is challenging to establish – should researchers locate near to competent services, or fund capacity-building if capacity does not exist, or strive to provide services themselves? Haire and Jordens (2013) insightfully noted that researchers' responses may have to include advocacy 'to call other parties to account' (p. 1). Data from this study suggests that ancillary-care guidance must help stakeholders to set limits on *engagement-based responses* – and this data (primarily from the first and fourth theme) suggests that two valued ways of setting such limits would be that engagement-based responses should (firstly) be proportional to participants' contributions *and* (secondly) not research-scuppering, even while they can be fairly demanding. Obviously such assessments will not constitute simple mathematical calculations - according to Richardson (2012) there is no 'simple ethical calculus' (p. 162). While such decisions will be qualitative (MacQueen & May, 2008; Richardson, 2012c) they do not have to be chaotic, *ad hoc* or completely intuitive (Richardson, 2012c). This point is revisited in the final chapter.

### 5.5.3 SITE-STAFF AND NETWORK INTERACTIONS

Practices described by network and local researchers for their mutual engagement indicate efforts to collaborate on the approach to care to be adopted in the trial. These practices are difficult to compare with practices from other studies because few have reported on this dyad specifically. It appears that network representatives strive to solicit the inputs of local investigators regarding how needs will be managed, to address the issues jointly and not to leave the 'moral burden of assessing ancillary-care claims and the logistical burden of planning for them in the hands of individual principal investigators' (Participants, 2008, p. 0710). For HIV needs, the network requires local researchers to delineate in some detail their site-specific approach, and provide inputs and assistance. Preparation of this so-called HIV treatment plan corresponds well with recommendations that there be proper planning for ancillary care needs (cf. Participants, 2008; MacQueen & May, 2008). In fact, planning has been referred to as the chief operational upshot of endorsing ancillary-care obligations (Meritt & Taylor, 2012). This data suggests that detailed written planning – at least for the endpoint – has been embraced by network and site-staff.

Certain site-staff questioned network practices regarding relying on site resources for addressing needs for contraceptive access and STIs – they questioned whether the network

should be doing more to help participants in this regard, even while recognizing regulatory restrictions regarding the use of research funds, and while expressing appreciation for their successes in mobilizing a treatment fund to enable coverage for ARVs for participants without national coverage. This raises the question of whether the network should implement the specific response of raising funds to provide medication for STIs, or to provide hormonal contraception for onsite dispensing so participants avoid time-wasting and poor service at referral sites? (Requiring contraception *per se* is a response grounded in safety because it avoids unknown harms to unborn children, but adopting a particular approach to prevent time-wasting and bad service for participants could be viewed as grounded in helping).

On the partial entrustment or whole person account researchers should not shoulder the burden of ancillary-care alone, and sponsors and network representatives should bear some of the burden of apportioned responses, and such responses can be fairly demanding but not research-scuppering. There is no formula for making this precise determination (Dickert & Wendler, 2009) but there should be pre-trial analysis to establish for example what financial burden this response would impose on the network (cumulatively across all sites) and whether it could be borne given their resources and power to leverage resources. A similar determination should be done for researchers at each site. It is worth considering whether the detailed written planning for HIV (the so-called HIV treatment plan that each site has to prepare) should be expanded to include other anticipated needs.

#### 5.5.4 **SITE-STAFF AND COMMUNITY REPRESENTATIVE INTERACTIONS**

Proponents of ancillary-care have alluded to the role of community in ensuring ancillary care. For example proponents of the 'Four Ps' approach have asserted that ancillary care plans should be developed in 'dialogue and partnership with the host community, in ways that maintain respectful interaction (...) and represent the population of potential participants, Community Advisory Boards and the local medical community' (Participants, 2008, p. 0712). Hyder and Merritt (2009) have argued that a study's package of ancillary care should be defined after a 'locally-driven deliberative process among concerned stakeholders' to elucidate their preferences (p. 430).

Practices described by site and network representatives to involve community representatives in protocol development, to involve site-level CAB members in protocol or materials review, to discuss with CABs the sites' approach to care, to respond to their *ad hoc* questions about care, and to seek CAB inputs on how to implement care approaches corresponded with recommendations to *dialogue* with host-community representatives about ancillary care (Participants, 2008). Site-staff practices reflected some effort to integrate community perspectives at various stages of trial design and implementation (Heise et al., 2008) as well as to hear suggestions for how care could be improved or delivered (Vallely et al., 2009). Reported practices did not include bargaining or negotiating with CAB representatives about additional substantive benefits as found in previous empirical explorations (MacQueen et al., 2008) or as recommended by some ethics commentators, namely that researchers should negotiate or bargain with participating communities to allow them to identify 'valuable' health-related benefits including ancillary care (Participants, 2004; Weijer & LeBlanc, 2006, p. 805/6). In future research into strategies for engaging community, perspectives about 'negotiating' with communities should be more fully explored, which is a point made again under recommendations for additional research.

Previous research has pointed to CAB presence and activity as a central feature of contemporary HIV prevention trials (MacQueen & May, 2008; MacQueen et al., 2008) although clearly engagement strategies should be more diverse and multi-faceted than CABs alone (MacQueen et al., 2012; UNAIDS/AVAC 2011; West Slevin, Ukpong & Heise, 2008). This study did not identify major concerns about insufficient practices to engage CABs in care decisions and implementation as found by Heise et al. (2008) but did identify subtle tensions and complexities with site-staff-community partnerships, detailed below.

*Firstly*, CAB members at some sites questioned not being allowed direct access to trial participants to explore participant experiences and respond to participant concerns. They questioned whether site-staff could be doing more to enable their access to participants. Proponents of ancillary care have recommended that the experiences of participants be actively gauged (Participants, 2008; Richardson, 2012c) and one helpful strategy may be to get CAB members to canvas such views – for example to explore the quality of the ancillary care approach. Direct access to participants by CAB members should only occur where

participants give permission for their identity as participants to be made known in this way, given need to respect confidentiality preferences (Emanuel et al., 2000; UNAIDS/WHO, 2007; 2012). Direct access to participants by CAB members should also only occur when CAB members are sufficiently familiar with HIV vaccine trials, and sufficiently trained to protect confidentiality, and more generally capacitated in accordance with recommendations for resourcing CABs (UNAIDS/AVAC, 2007; 2011; UNAIDS/WHO, 2007; 2012). Where the above cannot be guaranteed, presumably there are other strategies available to assess whether participants are in reality receiving the planned ancillary-care, such as monitoring by site-staff of whether participants take up direct and indirect care, and assessing the quality of their care experiences. Even where direct access by CAB members to participants is not permitted, CAB members can increase their visibility to participants through posters and contact details on consent forms. This tension does suggest that guidance on ancillary care should help stakeholders identify helpful strategies to get participants' feedback on their ancillary care experiences.

*Secondly*, site staff questioned the soundness of some community viewpoints, for example, requests for non-evidence-based care, and questioned whether such views should be 'allowed'. This empirically-identified complexity suggests that ancillary-care guidance should help stakeholders manage inputs solicited via consultation that might be inconsistent with sound ancillary care for participants. This concern supplements concerns about CABs already identified in the literature, namely that CABs can become co-opted by the research process (UNAIDS/WHO, 2006), can become dominated by political or other agendas, are financially dependent on researchers, have competing priorities in resource-limited settings (West Slevin et al., 2008) may lack representative and accountable members (Hankins, 2006) and may lack negotiating power (Haire et al., 2012). As set out in Slack (2014) this issue also appears inadequately addressed in current ethical guidelines which are generally silent about what should be done when solicited views conflict with other substantive norms, for example, to provide optimal care (UNAIDS/WHO, 2007; 2012; UNAIDS/AVAC, 2011). SA MRC (2003) gestures at this issue, setting out that community participation should enhance the 'ethical soundness' of an HIV vaccine trial, suggesting that inputs undermining 'ethical soundness' might be legitimately rejected. Ethical guidelines should take a stand about about how to proceed when inputs solicited in a consultation process conflict with substantive recommendations for ancillary care, as this might encourage even more active solicitation of

community views (Slack, 2014) which is a point made again in the next chapter. It is also possible that concerns about unreasonable inputs might explain the few 'negotiating' or 'bargaining' practices reported here.

This data suggests that efforts to engage CABs to improve ancillary-care decision-making and implementation should be continuous and even intensified (Slack, 2014). On several accounts of ancillary-care, researchers are encouraged to have a good understanding of the available care facilities and alternatives (Participants, 2008; Richardson, 2012c) and community consultation may provide researchers with a deepened understanding of the quality of these care facilities, which in turn will help them work out the precise response they should implement (for example, refer to such facilities or provide services onsite). Furthermore, on accounts of ancillary care that value reciprocating for participants' risks and burdens (such as partial entrustment and whole person accounts), it is possible that consulting community representatives may assist researchers to better understand *risks and burdens* assumed by participants from their perspective, for example, there could be risks, like stigma, that are culturally informed and hidden from researchers (cf. Dickert & Sugarman, 2005). On accounts of ancillary care (like partial entrustment and whole person accounts) that value concepts of *engagement* between researcher-participant, community consultation could enhance such assessments, for example there could be cultural factors influencing the intensity of the interaction between participants and researchers. Therefore, consultation with community representatives might make the analysis of key factors in ancillary-care accounts more precise, and influence the precise responses that researchers implement.

This data suggests that sites should create a space for critical reflection about policies for CAB/participant interaction (such as direct access to participants), and for formal review of ancillary-care approaches. The latter may be assisted by the better preparation of written materials about the site's approach (especially for non-HIV needs) to ancillary care – for example, a document entitled '*Our site-specific approach to helping participants get care for their medical problems identified in trials*' setting out in clear terms the proposed strategies. Formal space and time for reflection on the care approach with community representatives will go some way to achieve the openness about arrangements recommended by Richardson

(2012c). It would also go some way to discuss expectations, incorporate opinions and address concerns about ancillary care recommended by AVAC (2012) and will enable even more impact by community representatives on ancillary-care planning and implementation. It is also likely to consolidate trust theorized to underpin solid engagement (MacQueen et al., 2012). Network/ site representatives should also collate and distribute to affected CABs the care-related concerns identified by community representative in protocol-development in network and site-level discussions, and how they were addressed (Slack, 2014). These are points that will be returned to in the final chapter where recommendations for stakeholder practices are made.

#### 5.5.5 SITE-STAFF AND REC INTERACTIONS

Proponents of researchers' ancillary-care responsibilities recommend that planned responses to address needs should be in protocols and reviewed as an integral part of ethical review (Merritt, 2011; Participants, 2008; Richardson, 2012c). This study found that there were adequate statements in protocols about planned responses to HIV needs. This suggests that there may be a tendency to privilege care for the endpoint in protocol descriptions, with less written protocol statements about plans to address conditions of less scientific importance to the study (cf. Participants, 2008). However, this finding does show that at the very least plans for care for the endpoint are being presented to independent reviewers who can assess their appropriateness (Participants, 2008).

Protocols and supporting documents to RECs said very little about ancillary-care responses for conditions *other than HIV* even though site-staff undertook many such responses. This corresponds with results in earlier explorations in microbicide trials that site-staff do far more than protocols say they will do (Philpott et al., 2010). This study found that some site-staff and network representatives perceived that RECs' core mandate to approve protocols might prevent them from implementing flexible innovative but non-approved ancillary-care responses (Slack, 2014). This supplements previous findings that protocol omissions were driven by sponsor-restrictions on using research funds for care (cf. Heise et al., 2008; Philpott et al., 2010). Concerns about preserving flexible, nimble care responses are not anticipated in guidance, which tends to emphasize transparent declarations to RECs (Slack, 2014).

This data suggests that ancillary-care guidance will have to address perceived conflicts between transparency and flexibility. This data also suggest a tension between two ancillary-care approaches identified by Taylor et al. (2011) namely where researchers make decisions in advance of research conduct about participants' care (*a prospective response*) and where researcher make in-the-field decisions about how a particular participant's need should be addressed (*an ad hoc response*). It also suggests a tension between two levels of ancillary care deliberation identified by Merritt (2011) – namely for a particular protocol and for a particular person encountered in the implementation of a protocol. Ancillary-care guidance should address such tensions, and current ethical guidelines do not anticipate this. These are points that are revisited in the next chapter.

It is worth noting the omissions at the level of the protocol about planned responses to other needs (contraceptive, STI, general ailments) makes it difficult for RECs to judge the merit of the proposed strategies - which has been recommended by numerous accounts of ancillary care (Dickert et al., 2009; Participants, 2008; Richardson, 2012c). It is also worth noting that omissions in protocols or related supporting documentation become even more important if the mechanism via which stakeholders reach consensus on the care approach is through reviewing and making inputs to protocol/ protocol-related materials. Current ethical guidance recommends that consensus be achieved on the care approach prior to trial commencement (UNAIDS/WHO, 2007; 2012) and that stakeholders take part in an iterative transparent participatory process to come to such agreement (UNAIDS/WHO, 2007; 2012) yet guidelines do not delineate the form such processes should take (for example they do not mandate large consultative meetings). It is plausible that descriptions in protocols and related material spelling out how researchers plan to address needs identified in trials (not limited to HIV) could be reviewed by key groups such as CABs and RECs for their adequacy and acceptability, enabling a 'meeting-of-the-minds' to take place about the proposed approach. However this strategy for achieving consensus is imperilled if there is insufficient detail about care for key stakeholders to consider, object to, amend, or embellish. Of course, commenting on proposed approaches in protocols and related materials is best considered as one strategy to ensure that important constituencies weigh in on ancillary-care but other so-called 'innovative additional approaches' (Hankins, 2006, p. 031) may be needed to promote authentic communication about ancillary care (UNAIDS/WHO, 2006).

This study found that certain application forms from RECs were structured to elicit somewhat relevant descriptions of ancillary care, for example, some asked researchers to spell out 'benefits including clinical care', or 'benefits to participants', or 'whether the research involves health-care services'. However, the above statements could conceivably elicit statements about benefits associated with research procedures and not necessarily benefits associated with ancillary-care responses.

If more detail about planned ancillary-care responses is going to be called for then RECs may need to reassure researchers that there will be speedy review that allows researchers to respond to participants' medical needs in ways that may be non-approved (that is, not anticipated in the original protocol submission), thereby avoiding much-dreaded slow-turnaround times and time delays (Wassenaar, 2006) and promoting the much-valued timely feedback (Mamotte & Wassenaar, 2006). For example, it could be clarified whether such changes could be approved by Chair alone (and ratified later by a full committee) or whether they would have to be approved by a full committee.

This master theme indicates that a range of stakeholders are involved in responses to the ancillary-care needs of participants in trials suggesting that responses are apportioned between several role-players. In some instances stakeholders questioned whether their partners were doing enough. These findings suggest that ancillary-care guidance should set a threshold of costliness for researchers' engagement-based steps of other care stakeholders, so they can recognize when they have done enough to 'call other parties to account' (Haire & Jordens, 2013, p. 1) or done enough to try strengthen the capacities of such parties.

## 5.6 SUMMARY OF DISCUSSION

In summary, in this chapter master themes and sub-themes were discussed in terms of the existing literature. The first theme (*'Reciprocating, Engaging, Benefitting'*) showed that these stakeholders advanced 'pro-ancillary care' reasoning that is rooted in the relationship (variously characterised) - that suggests that relational accounts of ancillary-care may have traction with this set of role-players. Because interviewees do not always agree on what has

been contributed (requiring a reciprocal response), it would be helpful for ancillary-care accounts to provide some guidance about participant's contributions.

The second theme (*'Reconciling'*) set out that site-staff and network representatives implemented many helping-based, extra-scientific responses for participants – which at a minimum indicates that they are unlikely to reject accounts requiring such actions from them. Because site-staff experiences some conflict - when responses for science seemed to clash with helping participants with their important health needs - it would be helpful if ancillary-care accounts provided some guidance about what to do in such instances.

The third theme (*'Privileging'*) set out that there was within and between interviewee ambivalence about how much special treatment participants should enjoy, or how much responses for participants should deviate from responses for others (for citizens) – that is they were unsure about the 'dosage' of the response that should be implemented for participants. They also took steps that showed participants at some sites are privileged in relation to participants at other sites. They were also concerned about how much privileging should be publicly declared. This suggests that accounts of ancillary care should try to provide some guidance to stakeholders about 'privileging' or differential treatment complexities.

Theme four (*'Line-drawing'*) set out that stakeholders advanced reasons against unlimited ancillary-care responsibilities, but they had some concerns about whether their responses are totally adequate. This suggests that ancillary-care accounts should help trial stakeholders to set limits on their responses, and help them to recognize when they have done enough. Theme five (*'Partnering'*) set out that multiple role-players partnered for care, but sometimes the adequacy of partners' responses were questioned. This suggests that ancillary-care accounts should help stakeholders to set limits on their engagement responses – when have they done enough to try get partners to do their part?

These five themes suggest that these trial stakeholders were concerned with how to adjudicate between different moral parties such as participants versus citizens in the present; as well as 'here-and-now' participants versus future potential citizen-beneficiaries of

research. The following chapter revisits the three central aims of this study and draws conclusions about the implications of stakeholder experiences for ethical models and for ethical guidelines on ancillary-care.

# CHAPTER SIX

## CONCLUSIONS AND RECOMMENDATIONS

This study aimed to explore the ancillary-care experiences of stakeholders in HIV vaccine trials in South Africa – firstly to explore stakeholders’ practices and how they made sense of these practices, secondly to explore stakeholders’ contemporary concerns and complexities regarding ancillary care and thirdly to explore the implications of these experiences for current ethical guidance about ancillary care (both ethical models proposed in the literature as well as current ethical guidelines). This chapter sets out some concluding remarks in relation to these three major aims. Recommendations are made for ethical models, as well as current ethical guidelines; and for stakeholder practices. In the last section entitled ‘final remarks’ some final observations are made about whether the empirical findings may have been used, inadvertently, to lower ethical standards that might decrease protections for participants.

### 6.1 CONCLUSIONS

#### 6.1.1 STAKEHOLDER PRACTICES AND PERSPECTIVES

In terms of the first aim - to explore practices and perspectives - this study concludes that vaccine stakeholders endorsed that researchers have ancillary-care responsibilities towards participants’ medical needs, and viewed these largely in relationship-centered ways. For most stakeholders the idea of the researcher-participant relationship did much of the ‘heavy lifting’ in terms of underscoring why researchers should help participants with their medical needs. Within this, notions of ‘reciprocity’ were frequently and movingly invoked to justify responses for HIV needs. Notions of not-abandoning and not-using participants were also perceived as important reasons to address needs, as were notions of conferring service-related benefits on participants (see ‘*Reciprocating, Engaging, Benefitting*’).

Network and site-staff representatives were implementing responses for various identified needs (across HIV, sexual and reproductive health-care needs and other more general needs) that were beyond those required for scientific success and safety, that is, responses more correctly described as 'positive helping performances' (cf. Richardson, 2012c, p. 206). That is, for various medical conditions they took many steps to help, in addition to science-based steps in service of the protocol (see '*Reconciling*').

Network and site-staff representatives set limits on their helping-based responses (or their ancillary-care responses) by perceiving some needs as more important than other needs by virtue of their connectedness to the research question, and also by foregrounding their commitment to a deeply valued primary research mission that should not be undermined. They also apportioned responsibilities to other parties (see '*Line-drawing*'). Site-staff were engaged in various practices to form relationships with multiple stakeholders that they perceived as critical for securing care for participants (see '*Partnering*').

### 6.1.2 STAKEHOLDER CONCERNS AND COMPLEXITIES

In terms of the second aim - to explore concerns and complexities - this study concludes that stakeholders are grappling with several 'knotty complexities' about ancillary care (cf. Richardson, 2012c, p. 201). Stakeholders do not completely agree between themselves about what has been contributed by participants – is their effort, time, energy, bodies, volunteerism or risk-assumption? (see '*Reciprocating, Engaging, Benefitting*'). Stakeholders do not always agree on the most appropriate 'return' for participants' contributions, have some ambivalence about the degree of special treatment for participants relative to citizens, worry about special treatment leading to compromised decision-making, and implement responses for participants at some sites that advantage them in relation to participants at other sites (see '*Privileging*'). Occasionally site-staff encounter conflicts between science-based responses and helping participants with their important health concerns, such as concerns about contraceptive mandates over-riding participants' real wishes (see '*Reconciling*'). Also, sometimes stakeholders questioned the limits they have set on their helping-based

responses (see '*Line-drawing*') and the responses implemented by their partners (see '*Partnering*').

### 6.1.3 IMPLICATIONS FOR ETHICAL MODELS AND ETHICAL GUIDELINES

The section that follows sets out the implications of the study findings for leading models of ancillary care, as well as for ethical guidelines (UNAIDS/WHO, 2007; 2012; UNAIDS/ AVAC, 2011; SA MRC, 2003 and others). It does not make recommendations to revise guidance however such recommendations follow in a later sub-section.

#### 6.1.3.1 IMPLICATIONS FOR ETHICAL MODELS OF ANCILLARY-CARE

In terms of the third aim - to explore implications for ethical guidance - this study sheds some light on whether ethical models, as they currently stand, are likely to be perceived as relevant to affected stakeholders (Birnbacher, 1999 in de Vries & Gordijn, 2009).

Findings that relationship-centered reasons are often invoked suggests that models of ancillary care that rest on the researcher-participant relationship - such as partial entrustment or whole person - may be viewed as especially relevant by vaccine stakeholders, perhaps more so than accounts resting on responsibilities all persons have to all other persons independent of any relationship, such as rescue-based accounts. Findings that notions of 'reciprocity' are often invoked as reasons for care responses suggests that accounts resting (even in part) on reciprocity, or similarly gratitude, might also be experienced as relevant by vaccine stakeholders to their decision-making. These empirical findings do not of course settle conceptual debate about whether such models are substantively correct (cf. Grady et al., 2008) or superior to competing theoretical models.

Findings that many steps to help participants are implemented imply at a minimum that ethical models assigning researchers obligations to help participants with their care needs are

not likely to be rejected by them. Many of researchers' helping practices correspond with such models' recommendations. Several responses (such as establishing an HIV treatment fund, or hiring dedicated staff to address care needs) tend to exceed thresholds for 'not-inconveniencing' agents set out in rescue-based models, and reflect the response-threshold conceptualized by both leading models ('demanding but not excessively costly'). Findings that several responses exceed cost-thresholds of 'inconvenience' imply that vaccine stakeholders might embrace models of ancillary care that endorse such thresholds.

Findings that partnering is endorsed and undertaken imply that models that propose and guide apportionment of care responsibilities among role-players are likely to be viewed as relevant. Findings that stakeholder perceive that ancillary-care responses are not unbounded imply that models setting some limits and avoiding complete ancillary-care inflationism may be viewed as plausible (cf. Richardson, 2012c).

In one respect findings may imply that partial entrustment may be viewed as more convincing than the whole person model. More specifically, stakeholders perceived that needs centrally important to the aims of the research deserve more demanding ethical-review and addressing-needs responses than needs that are marginally important. This perspective appears to resonate with the notion advanced by partial entrustment that the degree of scientific importance of the need does matter when making ancillary-care decisions. However, this study cannot shed light on whether stakeholders endorse a view central to partial entrustment, namely that needs identified by study procedures should be privileged for researchers attention over needs identified by non-study methods (for example, by casual observation) because no relevant data was elicited.

Also in terms of the third aim, this study illuminates whether ethical models in their current form hold promise for resolving empirically-identified complexities. Findings about concerns and complexities imply that both leading accounts of ancillary care, both partial entrustment and whole person accounts, hold some promise for resolving these even without refinement (recommendations for refinement follow in the next section).

Regarding the issue of disagreement about *what has been contributed* by participants, both models attend to participants' various contributions, for example, positing that participants' permissions, cooperation, and willingness to assume risk and burden are relevant contributions, in a way that may help stakeholders to think more conceptually about such sacrifices. On the issue of an *appropriate 'return' for participants' contributions*, both leading models provide grounds for working out how demanding researcher responses should be, namely, both models assert that if gratitude is high, as well as other factors, such as engagement, then much is owed to participants, therefore these models would provide clear reasons for implementing a demanding response. Neither model allows for a simple calculation but both facilitate thinking-through what participants contribute, amongst other factors, and the range of appropriately 'dosed' responses.

Regarding concerns about *the degree of advantaging of participants relative to citizens*, both models provide a coherent way of defending 'differential treatment' of different classes of person. That is, responses are indexed to the degree of gratitude and engagement - which for citizens would be nil, for screen-outs would be less but not nil and for participants would be more than for either screen-outs or citizens. Put another way, both accounts contain the elements that could thoughtfully defend between-group differences in approach, therefore, they both hold out some promise for helping stakeholders with the issue. This approach - of implementing more demanding responses for classes of persons that have contributed more, or with whom researchers have interacted more, - corresponds with actual practices implemented for various groups in this study - where citizens received some care from researchers, but less than care given to screen-outs, which was in turn less than care given to participants.

Regarding the issue that *participants at some sites are advantaged over participants at other sites*, there is not much detailed writing on this complexity in either account, but technically the accounts themselves contain some elements that may assist with this. For example, if participants at some sites were likely to assume more risk - because of stigma, discrimination or violence against persons with HIV - then this might provide a defensible reason for implementing a 'response-with-more-return' for them because more would be owed to them on grounds of gratitude for uncompensated risks and burdens. Therefore the accounts

themselves contain the components that would allow considered decision-making about this, but they have not, to my knowledge, taken this issue on in much detail. Of course, the reasons for inter-site differences found in this study appear not to rest on additional risk or burden but rather appear to rest on contextual factors, for example, sites refer to facilities of varying quality. Accounts of ancillary care need to consider the acceptability of differences introduced by such factors.

On the issue of *whether researchers are doing enough to help*, there is direction in these accounts because both provide a threshold against which a response could be measured – namely ‘demanding-but-not research-scuppering’ – to ensure that ancillary-care obligations do not overwhelm the core duties of researchers. Therefore, technically both accounts could help stakeholders to weigh up each possible response and assess if the costs could be borne but these accounts do not say much about how to proceed if different stakeholders reach different conclusions about whether responses are reaching these thresholds.

Regarding the concern of *whether care partners are doing enough*, there is some limited direction in both accounts because these accounts presumably hold researcher steps to engage partners to the threshold for ancillary-care responses (‘demanding-but-not-research-scuppering’), however, this could be made far more explicit. It seems that while such accounts generally direct themselves to the conduct of researchers and sponsors these accounts might hold some research partner’s responses to a similar threshold (‘demanding but not primary-mission-scuppering’) therefore, for example, RECs should do enough to review planned ancillary-care responses short of undermining their own primary mission which is to review all protocols submitted for core ethical complexities. Regarding the issue of encountering ‘unreasonable’ ancillary-care requests from community partners, there is not much writing on this issue in either account. While both accounts acknowledge that consulting key stakeholders will be important there is little explicit direction on how to assess and manage ‘objectionable’ requests. However both models already contain the elements for adjudicating such requests, more specifically, an approach that is too expansive, unlimited or excessively costly could be rejected.

In terms of the Four Ps outlined in Participants (2008), namely 'positive duty', 'planning', 'pragmatic steps', and 'partnership', this study concludes that vaccine stakeholders recognised a strong *positive obligation* to assist participants with their medical needs. Researchers engaged in a detailed written *planning* exercise for HIV needs, assisted by the network, suggesting a high degree of prospective planning regarding how the endpoint will be addressed. In terms of '*pragmatic steps*', researchers implemented various practical responses for target needs (HIV) as well as non-target needs. In terms of *partnership*, researchers did more than merely partner with treatment-providers but entered into relationships with various stakeholders to address participants' needs, for example they engaged CAB members to assist with implementing care and they also engaged participants themselves in their own care.

Regarding concerns about *the degree of advantaging of participants relative to citizens* there is little substantive guidance on this issue in the Four P's approach - apart from cautions to be 'sensitive' to fairness issues between participants and others in need of care (Participants, 2008, p. 0711). On the issue of *between-site privileging* for participants enrolled in the same protocol, there is no guidance. On the issue of *line-drawing*, this framework allows that some responses, that outstrip funds, monopolise personnel time and interfere with the study objectives, could be rejected. On the issue of *partnering*, this framework does not explicitly address the issue that community partners, or others, might make requests for ancillary-care responses that are 'unreasonable' but, as above, the Four Ps framework contains elements that could help adjudicate such requests as outlined above where, for example, responses that undermine scientific goals might legitimately be precluded.

#### 6.1.3.2 IMPLICATIONS FOR ETHICAL GUIDELINES

In terms of the third aim - to explore implications for ethical guidance – these findings shed some light on whether current ethical guidelines (SAMRC, 2003; UNAIDS/ WHO, 2007; 2012; UNAIDS/AVAC, 2011) hold promise for resolving empirically-identified concerns and complexities.

The **UNAIDS/ WHO (2007; 2012) ethical considerations** in HIV prevention trials are not silent on many of the identified concerns and complexities. On the issue of *the degree of advantaging of participants relative to citizens*, these guidelines take a pro-privileging stance insofar as they recommend many more ancillary-care steps for participants than for screen-outs or citizens, and furthermore they recommend special steps for participants such as including them in priority lists for ART-access under 'Towards Universal Access' programs. UNAIDS/WHO (2007; 2012) explicitly provides some counter-arguments to offset concerns that better care for participants might lead to undue inducement and local inequalities, indicating that in their current form they do try to address such concerns, albeit briefly.

Concerns about whether *enough is being done to help* address participants' needs are partially addressed by existing text in UNAIDS/WHO (2007; 2012) but mainly for participants' HIV needs. This guideline explicitly states that researchers should take steps to integrate participants into treatment programs in their domestic setting *and* also implies that the standard in high-income countries is desirable in order to avoid different treatment standards between low and high-income settings. Therefore researchers might find answers to the question 'have I done enough to address needs?' by asking themselves if they have achieved these standards. Therefore these guidelines are not silent on line-drawing concerns (for HIV needs) but two standards are presented, without some text reconciling these. For sexual and reproductive health needs, researchers are encouraged to strive for 'appropriate' care, but for general needs it is hard to find answers to questions about line-drawing in UNAIDS/WHO (2007; 2012) because not much is said.

Regarding concerns about *whether care partners are doing enough to help*, UNAIDS/WHO (2007; 2012) provides little guidance. It assigns ancillary-care responses to non-researchers, for example, local service-providers are assigned primary responsibility for care; RECs for reviewing care; communities for participating in discussions amongst others, but these guidelines do not set explicit limits on researchers' engagement practices, therefore readers of the guidance may not know if enough has been done by researchers to encourage partners to meet their responsibilities.

UNAIDS/WHO (2007; 2012) highlights HIV needs by having an explicit guidance point on care for HIV needs, mentions sexual and reproductive health needs in various places, and alludes to more general needs. The guidelines also recommend a range of ancillary-care responses for participants such as planning, providing some services directly, referring for care, collaborating with service providers, integrating trials into national HIV care approaches, and informing participants about HIV care. Findings about practices, largely set out under 'Reconciling' and 'Partnering' indicate that many guideline-recommendations are being met (cf. Slack, 2014).

The **UNAIDS/ AVAC (2011) good participatory practice guidelines** in their current form are also not silent on several concerns. Regarding concerns about *the degree of advantaging of participants relative to citizens*, these guidelines take a limited pro-privileging stance - namely they recommend discussion of 'priority access' to national treatment programs for participants (p. 53). On the issue of *between-site privileging*, these guidelines allow that non-HIV care packages may vary from site to site depending on local priorities, providing some guidance to stakeholders that cross-site differences in care may be defensible if based on principles such as respect for community health priorities. On the issue of *whether enough is being done* to address needs, these guidelines outline a standard for HIV care (namely 'comprehensive care including ART regimens') against which responses could be measured for HIV needs, but there is less direction for line-drawing concerns for non-HIV needs. On the issue of *whether care-partners are doing enough*, UNAIDS/AVAC (2011) recommends that care responsibilities be shared out and recommends discussion of care which might foster the conditions for critical reflection about each partner's contribution, but no threshold is set for researchers' engagement-based ancillary-care responses. UNAIDS/ AVAC (2011) recommends researchers 'negotiate' with community representatives about care, but gives little direction on what to do when inputs appear 'unreasonable', therefore stakeholders grappling with that particular problem might not find much help here.

Lastly, UNAIDS/AVAC (2011) has guidance points dedicated to HIV-care *and* non-HIV care – alerting stakeholders to the broad range of needs likely to be encountered in trials, and these guidelines helpfully set out various responses that sponsors and researchers should implement for care, including discussing various elements of care with stakeholders, and

ensuring sufficient funding for care. Many responses identified in this study under 'Reconciling' and 'Partnering' correspond with many of these recommendations (cf. Slack, 2014).

The SA MRC (2003) ethical guidelines for HIV vaccine trials in South Africa have text that partially addresses identified concerns and complexities. Regarding concerns about *the degree of privileging of participants over citizens*, this guideline prioritises participants for some steps over citizens (access to an ART regimen) suggesting it has little discomfort in privileging participants over non-participants for some care aspects. It also explicitly notes that steps for participants may be incentives and may introduce local inequalities and provides some brief counter-arguments. On the issue of *across-site privileging* there is little to assist stakeholders in the SA MRC (2003) guidelines. Concerns about *line-drawing* or whether enough is being done to ensure care might be partially addressed here for HIV needs because the guideline sets a standard for researchers to aspire to ('high quality' treatment that includes ART) but there is less help about line-drawing for non-HIV needs. There is some limited guidance relevant to the issue of whether *care-partners are doing enough* because this guideline recommends 'a continuing forum for communication and problem-solving' (p. 11) which might facilitate critical reflection on each care partner's contribution to care. However, this guideline tends to privilege 'community' partners out of the full spectrum of stakeholders impacting on care, and no threshold is set for researchers' engagement practices.

While not specific to South African HIV vaccine stakeholders, the HPTN (2009) guidelines do contain text that speaks to certain concerns and complexities. Regarding concerns about *the degree of privileging of participants over citizens*, there is - on the one hand - text that appears to support differential treatment of participants versus citizens based on participants' uncompensated risks and burdens and the depth of the researcher-participant relationship. On the other hand, there is text that cautions against worsening in-country inequalities. Therefore the tension between privileging and avoiding inequality is flagged but there is little text to help stakeholders resolve this tension. Regarding issues of *line-drawing*, HPTN (2009) refers firstly to actual responses to implement such as planning and partnering, and secondly to a threshold of costliness against which responses can be judged namely 'costs to the researchers (in money, personnel or study power)' (p. 50). These guidelines, thirdly, set a

standard to reach for, namely, to meet local standards and to seek to enhance services where standards are low. On the issue of *whether partners are doing enough* to impact on ancillary care HPTN (2009) recommends dialogue and collaborative decision-making with stakeholders about care which might include active reflection about each stakeholder's performance.

Finally, these guidelines alert readers best of all to the reality that researchers will encounter many needs in trials (not limited to HIV). These guidelines recommend a series of helpful responses such as understanding likely needs, understanding existing alternatives, strengthening local capacity, entering into partnerships with care-providers, informing participants about care they will receive (including services related to the science/ safety of the trial and services purely to benefit them), and declaring care for reviewers. Many implemented steps, under '*Reconciling*' and '*Partnering*', correspond with these ethical recommendations.

Taken together, existing ethical models and guidelines are not silent on many empirically-identified concerns and complexities, indicating their continued relevance to contemporary issues. However on some concerns there is little direction, or available direction could be refined and reformulated to be even more responsive, which is the subject of the following section.

## 6.2 RECOMMENDATIONS

In this section various recommendations are made for revising ethical guidance, largely about how to be more responsive to ethical concerns and complexities identified in this study. Concrete recommendations are made for various stakeholders involved in ancillary care.

### 6.2.1 RECOMMENDATIONS FOR ETHICAL MODELS AND ETHICAL GUIDELINES

In this sub-section suggestions are made for how ethical models and ethical guidelines could be refined to strengthen their relevance to stakeholders in the field, and to strengthen their ability to respond to complexities *even better than they currently might*. It begins with leading models of ancillary care and follows with current ethical guidelines.

#### 6.2.1.1 RECOMMENDATIONS FOR MODELS OF ANCILLARY CARE

This study suggests that ethical models of ancillary care could be more fully elaborated so that they are even more responsive to stakeholder complexities (c.f. Carter, 2009; Braddock, 1994 in De Vries & Gordijn, 2009). As set out in the previous section, there is much in the current leading accounts of ancillary care that stakeholders might perceive as relevant and responsive to complexities, however, it also seems that some elaboration of these accounts might further strengthen their overall helpfulness in this regard.

In terms of leading accounts of ancillary care – namely the partial entrustment and whole person accounts - the factor of ‘gratitude’ might be better named as that of ‘indebtedness’ because it seems to resonate more closely with perceptions elicited in this study, and the term ‘indebtedness’ also seems to resonate with how the factor is characterised in the literature (Richardson, 2007, 2008, 2012c). Also, it may help if the partial entrustment and whole person accounts could incorporate ‘proportionality’ as a possible limit-setting factor to complement the current limit-setting factor of ‘costliness’. If this was done more explicitly than is currently the case, then ‘disproportionateness’ as well as ‘excessive cost’ could both constitute legitimate ways to decide on the strength or ‘dosage’ of a particular ancillary-care response. Given that stakeholders in this study were concerned about getting the ‘dosage’ of their responses correct, having two notions against which to evaluate appropriate responses may be of some conceptual assistance. The models should make some recommendations for how to proceed when stakeholders do not agree on the whether responses are ‘proportional’ or ‘excessively costly’.

In addition, these models should also explicitly address the issue of between-site differences for participants enrolled in the same protocol, although elements of the account already provide some clues for how this could be justified. For example, if participants at one site assume risks that participants at other sites do not, then such differences could be defended. These accounts should explicitly consider the acceptability of differences introduced by contextual factors such as varying quality of available referral centres.

Furthermore, these accounts should more explicitly address the issue of how to adjudicate requests about ancillary care that do not rest on, or even undermine, core factors, for example, could requests from community representatives (or anyone for that matter) that appear disproportionate to contributions, or excessively costly, be legitimately rejected? It seems to follow logically from central elements of the accounts, but more explicit attention should be given to this. Current recommendations that decisions be made in consultation with key stakeholders would be more convincing if they addressed this issue head-on.

Findings that network and site-staff representatives have concerns about committing ancillary-care responses to paper suggest there may be tension between two levels of ancillary care responses identified in the literature – the prospective response and the *ad hoc* response (Taylor et al., 2011; Merritt, 2011) whereby planning upfront in protocols was perceived to undermine flexible ‘in the field’, ‘on the spot’ decision-making and this tension should be addressed in future debates about ancillary care.

Findings that some site-staff are concerned about science-based steps not helping participants should also be addressed in future discussions of ancillary care. In this study, these were related to enrolling participants into future protocols, ensuring that participants to take reliable contraception and counselling participants to access abortions. Models of ancillary-care tend to focus on researchers’ responsibilities to implement helping-based steps and less on science-based steps, but some consideration of how to implement science-based steps more helpfully may be useful. For example, it is possible to extrapolate from central features of ancillary-care models that when researchers face such troubling situations they

should implement responses that are 'demanding but not excessively costly'. Such responses include identifying where unhelpful practices may be operating, refraining from implementing these, replacing these with more helpful responses (in this case, more sensitive enrolment procedures and more sensitive counselling practices for contraceptive uptake and termination of pregnancy uptake) and ensuring that staff are in place who can sample these troubling situations and act as participant advocates. Finally, these models should declare more explicitly that researcher steps to engage partners are held to the same threshold for ancillary-care responses ('demanding-but-not-research-scuppering').

Recommendations for the 'Four P's' include that a revision paper should take on some of the empirically-identified complexities in a more 'head-on' way. How should stakeholders who are committed to participants' care address their concerns about citizens not being advantaged apart from merely being more 'sensitive'? Does it matter if participants at some sites receive a more expansive ancillary-care approach than at other sites?

#### 6.2.1.2 RECOMMENDATIONS FOR ETHICAL GUIDELINES

In this section recommendations are made for each ethical guideline separately to increase the ease with which feedback could be given to each guideline-development group. Making recommendations for revised guidance does raise the tension about whether guidance should be granular (Krubiner, Sayed & Merritt, 2014) or left intentionally somewhat vague to enable different determinations to be made depending on the circumstances (Macklin, 2012).

What recommendations would logically follow from a study such as this for international ethical guidelines governing HIV prevention trials specifically? In terms of the **UNAIDS/WHO (2007; 2012) ethical considerations** this study provides some idea of how this guideline might be revised to strengthen its responsiveness. The brief reference to 'justice as reciprocity' as a justification for ancillary care should be expanded to provide more direction on the essential contributions made by participants, the need to consider carefully responses that are proportionate to these contributions, the need to try to achieve agreement about these proportional responses, and the need to revise responses in line with evolving

information about the risks, burdens and sacrifices assumed by participants (or even volunteers for that matter). In the guidance point on care and treatment, readers should be alerted to the relatively broad range of needs likely to be encountered in trials, even by current study procedures, because the guidance point currently focusses almost exclusively on HIV.

Guideline-developers for UNAIDS/ WHO (2007; 2012) may wish to add some text that alerts readers that occasionally researchers may experience conflict (a clash) between science-based responses versus helping participants with their important health needs, and that recommends that such incidents be collated as part of an overall commitment to regular reviews of ancillary-care approaches.

Revisions should also explicitly address the issue of differences between care at various sites because currently readers have to infer a stance from the stance on between-nation differences, namely striving for equivalent standards. Current text about the issue of undue inducements (see benefits guidance point) should be expanded to recommend the implementation of enhanced consent strategies to ensure processing of risks as well as rigorous review by RECS and community advisors to reduce risks to an acceptable level. This might help to further address undue inducement concerns while ensuring that such concerns do not uncritically trump ancillary-care responsibilities. Expanded text on participants' contributions, as recommended in the paragraphs above, may help stakeholders decide which responses are more or less proportional to participants' contributions, providing stakeholders with a way to carefully consider the 'dosage' of ancillary-care responses for participants.

Revisions should clarify the issue of how far researchers should go to address needs. For participants with HIV, the tension between the two presented standards should be more explicitly addressed, namely integrating with treatment programs in domestic settings while striving for treatment in high-income settings. For example, these guidelines could clarify that national treatment is the 'floor' and international treatment is the 'ceiling' to strive for by implementing additional ancillary-care responses such as advocacy to improve treatment

nationally, or by directly providing care elements lagging behind in national programs such as procuring third-line drugs for resistant HIV.

Revisions should consider including guidance modelled on recent accounts of ancillary care that do not necessarily set a standard for researchers to strive for but rather recommend that researchers implement ancillary-care responses that do not exceed a certain costliness threshold such as a 'demanding but not excessive' threshold (cf. HPTN, 2009; Richardson, 2012c) as well as implement responses that are inherently proportional to contributions. This approach might help stakeholders with line-drawing concerns for needs more generally, not limited to the endpoint. Guideline drafters considering the best approach should recognise that the latter approach asserts that participants deserve care responses that are not excessively costly and are proportional to contributions, even though these responses may not necessarily ensure care mirroring that available in high-income settings *in all respects*, because this might fail the 'tests' of cost and proportionality. Regardless of the approach adopted, the UNAIDS/WHO guideline revision should provide more direction for line-drawing concerns for non-HIV needs.

UNAIDS/WHO (2007; 2012) recommendations to declare services and ancillary interventions in protocols should be retained but refined to incorporate concerns about preserving nimble innovative responses, and not merely prioritise transparent declarations to RECs as it currently does. These guidelines should also provide some advice about how to proceed when inputs solicited in a consultation process conflict with substantive recommendations for ancillary care, as this might encourage even more active solicitation of community views (Slack, 2014). Consent recommendations should be revised so that they do not privilege understanding of HIV care alone. Rather, they should recommend more broadly that participants understand how their needs will be addressed (not limited to HIV), and that participants should understand responses stemming from the scientific protocol, as well as responses associated with helping efforts by the site. In this regard, the recommendations of the HPTN (2009) guidelines offer sound direction.

What recommendations would logically follow from this study for the **UNAIDS/ AVAC (2011) good participatory practice guidelines**? These guidelines endorse 'negotiating' the range of

non-HIV services with stakeholders, which was an approach discussed in this study as being complex if 'unreasonable' views are solicited. Therefore revisions should engage with these concerns and set out how to reject requests based on non-arbitrary reasons, for example, where the request is for a response that will undermine the scientific integrity of the trial imperiling results that may benefit future persons. Because consent recommendations privilege understanding of HIV care, they should be expanded to recommend comprehension of the care approach for various needs that will be implemented at the site. A threshold of costliness for ancillary-care responses, including engagement responses, might be helpful.

What recommendations would logically follow for national ethical guidelines governing HIV vaccine trials specifically? The SA **MRC (2003) ethical guidelines** omit reasons for ancillary-care that are based on reciprocating for risk/burden/contribution viewed by these stakeholders as fairly powerful reasons underpinning responsibilities to implement ancillary-care responses. Revisions should include some explication of the notion of reciprocity because it seen as relevant by stakeholders as well as by ethical commentators writing about ancillary care, and may help stakeholders make decisions about appropriately 'dosed' responses.

SA MRC (2003) tends to focus on the condition of HIV, and does not highlight sufficiently that researchers will encounter various needs in trials and should consider their helping responses for these needs. As such the recommendations in this guideline are somewhat narrower than the actual ancillary-care responses implemented by site-staff for non-HIV conditions and narrower than the recommendations from leading scholars (MacQueen & May, 2008; Richardson, 2012c). Therefore, SA MRC (2003) should be revised to reflect the broader range of needs likely to be encountered. SA MRC (2003) consent recommendations also focus on care for HIV, while they should recommend that participants have a broader understanding of the ancillary-care responses researchers will implement for them for various needs identified in trials. SA MRC (2003) should also be updated to keep pace with more recent understandings that engagement involves a range of critical stakeholders including but not limited to participating community (cf. UNAIDS/AVAC, 2011). Text could also be added to help stakeholders with line-drawing concerns for non-HIV needs.

The HPTN (2009) ethical guidelines are intended to guide the conduct of HPTN-affiliated researchers, and therefore it may seem a stretch to consider how these guidelines might be revised to better address complexities identified here. However, given their popularity and reach, it seems to be an omission not to do so. It is possible that readers might experience some conflict between recommendations justifying differential treatment of participants with HIV versus recommendations to not worsen in-country inequalities, therefore, some text bridging these two stances may help. For example text could read *'While there may be grounds for ensuring participants receive some care that is not available to citizens on grounds of participants' risks/ burdens and engagement with researchers, efforts should be made to ensure differences in the care approach are well-justified and sufficiently explained to critical stakeholders'* or words to that effect. HPTN (2009) has comprehensive guidance on partnering that might be further strengthened if recommendations were made to consider tensions and trouble spots between partners and to commit to performance reviews of all partners.

National guidelines (SA DOH, 2004) - that govern all research conducted within the borders of South Africa – currently endorse equivalency between participants in low and high-income settings, while discouraging a narrow focus on mere access to drug regimens, and conceding that complete equivalency is unlikely. In addition to recommending certain ancillary-care responses as they currently do (that researchers improve conditions and garner support from developed-country parties), these guidelines should recommend additional ancillary-care responses such planning for how needs will be addressed, reviewing such plans by local review bodies, and communicating such plans to participants; amongst other recommendations. These guidelines should set out more explicitly that researchers will encounter various health needs while conducting research, and should foreground that researchers have positive, welfare-promoting reasons to implement ancillary-care responses.

It may assist if all the ethical guidelines considered conceptualising potential risks of participation *not only as* things to be minimized or offset by foreseeable benefits (that is, offset by direct compensating benefit for beneficial procedures; and offset by knowledge for non-beneficial procedures) - as they currently do - but *also as* things to be reciprocated by researcher ancillary-care responses. If this approach was deemed to have merit, as indicated

by Macklin (2006a) and Dickert et al (2009) and Richardson (2012c), guideline-developers could add text to this effect in sections on risk, with a cross-reference to sections on ancillary care. It will also help if all the ethical guidelines make more effort to conceptualise and define burdens related to trial participation, as opposed to risks of trial participation (cf. Ulrich et al., 2005).

## **6.2.2 RECOMMENDATIONS FOR PRACTICES**

In this sub-section recommendations for strengthening practices are made separately for various stakeholder groups in order to make it easier to give feedback to various ethical actors in the ancillary-care enterprise. Practical recommendations for amending practices are important because more responsive guidance alone may not automatically translate into improved practices.

### **6.2.2.1 RECOMMENDATIONS FOR RESEARCHER AND NETWORK PRACTICES**

Site-staff and the network should continue their commitment to the detailed planning process already implemented for HIV needs, and consider expanding this to include non-HIV needs, in line with recommendations that planning should not be limited to care for the endpoint (Participants, 2008; Richardson, 2007). Network representatives should continue to implement the specific ancillary-care response of having a treatment fund for ARV drugs if participants cannot access these nationally, because this response is targeted against plausible gaps in national programs, such as inadequate domestic access to third-line drugs for resistant HIV or possible stock-outs of ARVs, is perceived as helpful by site-staff, and is consistent with the application of leading models (Richardson, 2007).

Site-staff should continue to implement ancillary-care responses for medical needs they identify, but findings from this study suggest it would help to hold regular reviews of, or reflections on, their ancillary-care approach at sites, including space for reflection about 'critical incidents' where scientific responses are perceived to clash with helping participants

with their important health concerns, and where ancillary-care responses are perceived to clash with scientific integrity. Such 'tricky cases' should be collated and distributed. There should also be inter-site communication to raise awareness of approaches being adopted at other sites, so that between-site differences can be carefully weighed. Site-staff should carefully defend the approach adopted at their site based on clear substantive grounds, and should regularly assess the quality of all strategies being implemented at their site. These recommendations would go some way to operationalize existing recommendations that care approaches be actively assessed (UNAIDS/WHO, 2007; 2012).

In order to promote ethical review of ancillary-care responses as recommended by various commentators (Participants, 2008; Richardson, 2012c), network representatives involved in drafting template protocols should create standardized text or 'boilerplate' that speaks in a generic manner to ancillary-care for identified needs, not limited to HIV. Likewise, researchers at various sites should do more to declare their specific, non-generic, ancillary-care approach for such needs in written documents to the REC. To address concerns identified in this study about flexibility, researchers should draft such documents in ways that are adaptive to possible changing conditions at sites, for example, '*At this site, STIs will be addressed by onsite treatment or by referral to public sector should the former strategy not be possible*'. Researchers should consider declaring ancillary-care approaches in site-level documents such as a 'Site Bill of Rights and Responsibilities' that can be regularly reviewed and easily amended. These actions would help to operationalize recommendations in models that RECs judge the adequacy of proposed ancillary-care responses (Participants, 2008; Richardson, 2012c).

Researchers at various sites involved in adapting consent forms should make sure that proposed approaches to care are stated (but phrased in a way that facilitates flexibility) so that these statements can be integrated into meaningful discussion with participants about how their needs will be addressed to promote a coherent understanding of planned ancillary-care responses. Such steps will help realize recommendations that participants understand the broad care approach (HPTN, 2009) as well as the implications of participation (Lindegger & Richter, 2000).

Researchers and network representatives should continue and intensify their efforts to engage CAB members to improve care decision-making and implementation, by creating periods for critical reflection on how they are interfacing with CABs, how CABs are interfacing with participants, and how CABs are interfacing with key documents like protocol/ protocol-related material, and by preparing materials that better set out ancillary-care plans in order to solicit inputs from community (cf. Slack, 2014). Researchers should plan carefully for, and even discuss with communities, how they will decide to reject requests based on clear, substantive, non-arbitrary reasons. Such actions may go some way to express the spirit of transparent, trusting relationships promoted in good participatory practice guidelines (UNAIDS/ AVAC, 2011).

#### 6.2.2.2 RECOMMENDATIONS FOR REC PRACTICES

RECs have a critical role to play in helping researchers shape their ancillary-care responses (cf. Richardson, 2012c). However, RECs should amend their own practices to more forcefully impact on ancillary-care. They should try to elicit good information from researchers about their plans, and their application forms should be amended to elicit better descriptions about the issue at hand, for example such forms could include a question like *'describe here how you will help participants address medical needs identified or encountered in trials, even when this forms no part of the scientific protocol you are pursuing'*? (cf. Richardson, 2012c in Slack, 2014). RECs should debate how they can adapt their own procedures to ensure timely review of amendments to protocol-related descriptions of planned responses, based on concerns from researchers about being 'locked' into approved responses.

They should also regularly review their own performance of ancillary-care review. They should try to build in some time for substantive debate about ancillary-care responsibilities, even while respecting that review of ancillary-care concerns should not necessarily trump review of the multiple, complex, demanding ethical concerns in HIV prevention trials. These actions should help realize specific ethical recommendations that RECs carefully assess ancillary-care responses (Participants, 2008; Richardson, 2012c) and more general recommendations for independent, 'arms-length' review of key components of trials (Emanuel et al., 2008). By reviewing protocols for compliance with major ethical

recommendations and norms, RECs are well placed to increase the impact of ethical guidance. Specific focused training for RECs about researchers' ancillary-care responsibilities (and their own review responsibilities) should be undertaken.

### 6.2.2.3 RECOMMENDATIONS FOR CAB PRACTICES

CABs should request better written materials about the sites approach to ancillary care (especially for non-HIV needs) – for example, a document entitled '*Our site-specific approach to helping participants get care for their medical problems identified in trials*' setting out in clear terms the proposed strategies. CABs should continue to make inputs about the adequacy of the ancillary-care approach because they are they are likely to possess information that makes them especially well-suited to this, for example possessing first-hand knowledge of conditions at proposed referral sites. CABs should make requests of site leadership for more space for careful reflection on ancillary-care approaches at sites, as well as related approaches - such as whether CABs should approach participants directly to canvass their ancillary-care experiences (and receive the requisite capacity-building to protect the necessary confidences). They should request that all community-inputs made during protocol-development, both at the network-level and at the site-level, be collated and distributed to consolidate and profile key community perspectives on ancillary care. These steps will likely enable this key stakeholder to assess and even improve the ancillary-care approach at sites, as well as foster trusting site-CAB interactions as promoted by key guidance documents (UNAIDS/ AVAC, 2011). Training for CABs should address this critical issue, as part of site start-up activities, and ongoing capacity-development activities.

### 6.2.2.4 INTER-STAKEHOLDER RECOMMENDATIONS

It is possible that certain of the tensions identified here, such as equivocation about what participants contribute, what are appropriately dosed responses, how much privileging over citizens is acceptable, how much privileging between sites is acceptable, how to draw the line around ancillary-care responses – including engagement practices, could be expressly

debated in inter-stakeholder forums. However, it is important that such deliberations do not take place in a vacuum (Participants, 2008) but are guided by some normative framework.

Findings from this study suggest that the partial entrustment or whole-person frameworks might helpfully frame such discussions because of their recognition as relatively developed accounts (cf Merritt, 2011) and because features of the models appear to lend themselves to resolving certain complexities identified here, and finally because perspectives identified in this study suggest aspects of these models may be viewed as relevant. Of course, empirical findings alone cannot necessarily definitively settle the debate about which argument will 'carry the day' (cf. MacQueen, 2010). Such inter-stakeholders forums should be conducted more than once, to keep up with relevant contextual events such as data from other trials about risks and burdens assumed by participants, changes in care available to regular citizens, the development of new sites, and dynamic partnerships.

Also, if ethical recommendations from current guidelines and models were summarized and disseminated among vaccine stakeholders it may assist stakeholders to judge their own conduct, and their partners, more critically. It would also ensure that guidance better 'penetrates' various communities.

### 6.2.3 RECOMMENDATIONS FOR ADDITIONAL RESEARCH

These major themes could be explicitly explored in further qualitative research, because the study interview schedule was not structured around them.

Under '*Reciprocating, Engaging, Benefitting*', it may be helpful to explore whether stakeholders perceive that researchers have responsibilities to participants that are not located in the researcher-participant relationship but are in fact rooted in non-relational obligations, because this distinction is important to various accounts of ancillary care. Additional data should be gathered about stakeholder perceptions of the concept of participant burden (including restrictions) as opposed to risks, because this distinction is

alluded to in ethical models and ethical guidelines, but there is little data about how vaccine stakeholders make sense of the distinction. Detailed qualitative explorations of how ancillary-care obligations are framed in other (non-HIV vaccine) trials and research settings would be helpful to establish whether the salience accorded to reciprocity by these stakeholders holds elsewhere. It may also be useful to explore whether stakeholders *across various research contexts* merely 'rank'/ 'weight' rationales (or factors) differently, or whether they invoke entirely different rationales. This may partially inform conceptual debate about whether ancillary-care frameworks should be general with context-specific application, or whether specific frameworks should be advanced for different research contexts.

Under '*Reconciling*', it may be helpful to explore other specific critical incidents where researchers and site-staff perceive that responses being implemented for the science do not help participants with their important health concerns. While strictly not an issue of ancillary care, these study findings suggest this is an important part of stakeholders' care experiences and as such should not be ignored by guidance-drafters.

Under '*Privileging*', future research should explore in much more detail perceptions about the 'dosage' of responses or extent of benefits for participants in relation to non-participants perhaps structured around certain scenarios. This may be a promising line of further empirical inquiry given that it was identified here as a critical complexity and given that the issue of proportionality occupies an important place in several accounts of ancillary care. Perceptions about declaring such advantaging in written material should also be more fully explored, for example, whether omissions might be linked to concerns about the therapeutic misconception, because this is currently not clear.

Under '*Line-drawing*', future research should explore whether stakeholders see it as relevant to ancillary-care responses whether researchers encounter needs via actual study procedures or through non-study methods, such as naked-eye observations or mere knowledge of prevailing problems. This is an unanswered question, and the distinction is one of theoretical relevance to the partial entrustment account of ancillary care (with its emphasis on scope). It is also possible that direct observation of actual trial procedures such as general physical examinations and medical history-taking (that take place at regular intervals through-out the

course of these trials) may yield a wealth of information about how it is that medical needs are identified or uncovered during such trials.

Future research should also explore in more detail other countervailing considerations raised by interviewees, such as the burden of shouldering legal responsibility for participants' care. It should explore other 'critical incidents' where stakeholders wonder if more could be done to help, or where they fear that helping-based responses might undermine scientific integrity. Lastly, future research should explicitly explore with vaccine stakeholders which approach to line-drawing in ethical guidance appears more helpful - an approach that recommends that researchers ensure care reaches a certain standard in a particular setting (as implied by UNAIDS/WHO, 2007; 2012), or rather an approach that recommends researchers implement responses that do not exceed a certain cost-threshold (as suggested by Dickert & Wendler, 2009; Participants, 2008; Richardson, 2007). Again, stakeholder perspectives would not settle debate about which approach is conceptually more rigorous, but would merely indicate which approach is perceived to provide clearer assistance in the field, or what guidance stakeholders fall back on, which could be factored in to further conceptual work.

Under '*Partnering*', future research should explore stakeholders' views and practices regarding community requests about ancillary-care responses, for example, strategies for recognising and rejecting so-called 'unreasonable' inputs. Such research should explore whether such rejections are done on rigorous grounds, for example, based on proportionality considerations invoked by these stakeholders and contained in current ethical approaches (cf. Richardson, 2012c).

Finally, this study did not explore qualitatively the issue of stakeholders' actual knowledge of ethical guidance, which should be undertaken in future research, as part of efforts to improve the impact of guidance. Also, future research should directly ask stakeholders about how helpful they perceive the ethical guidelines to be on each of these major thematic concerns to supplement observations about the likely helpfulness of such guidelines made in this study. However, innovative research designs will be needed for such explorations.

Future research should access trial participants because this study did not access the views of this critical group, due to anticipated onerous special review requirements. Participants could be asked questions linked to major themes identified here such as whether they experience tensions from community members related to privileging, and whether they perceive researchers to be drawing the line correctly. Their perspectives are likely to represent a useful and untapped set of perspectives about this complex issue.

Interviews with sponsors of clinical trials would be a critical component of future research to explore whether they perceive themselves to have positive obligations to implement ancillary-care responses (despite regulatory restrictions, where this is relevant), and to explore their ancillary-care practices if any. Representatives of referral sites will be an important future source of perspectives, for example, about the issue of whether responses adopted for participants impact negatively in any way on general citizens.

Future research should include the strategies of observation of relevant trial processes impacting on ancillary-care, such as vaccine discussion groups with community members; consent discussion groups with pre-participants; individual consent discussions with actual participants; trial visits including general physical examinations and medical history-taking; and even outreach activities by community liaison staff to referral centres.

While REC representatives were interviewed and key correspondence reviewed, this research did not access adverse event reports which could provide a useful window into how sites respond to medical needs identified in trials (Richardson, 2012c). Comparing planned responses in protocols with actual responses set down in adverse event reports may shed some light on whether researchers do ever implement different responses from the ones they declared in their protocol submissions.

### 6.3 FINAL REMARKS

At the outset of this study, it was clear that considerable debate existed about the ancillary-care responsibilities of researchers, including the reasons that researchers have responsibilities and the extent of their responsibilities. Several influential ethical frameworks in the conceptual literature delineated ancillary-care responsibilities, and leading ethical guidelines made recommendations in this regard, including about why such needs should be addressed and the responses that should be implemented, including various engagement practices. There was prior work documenting the ancillary-care conduct of HIV prevention researchers, as well as researchers in other fields, but less work detailing perceived complexities and concerns, and even less work considering the implications of this empirical data for ethical guidance, and even less work considering whether current guidance spoke adequately to current complexities.

This study aimed to explore how vaccine stakeholders implemented ancillary-care responses, how they made sense of such responses, what their contemporary concerns and complexities were, and to consider the implications for ethical guidance. This study found that current ethical accounts, and ethical guidelines, might provide some guidance on certain concerns and complexities but could be amended to do so *even better*. Ethical guidance is often deliberately formulated at a fairly abstract level because it cannot anticipate all concrete situations, however, this study indicated several concerns and complexities that guidance-drafters may wish to consider in future iterations of guidance to ensure revisions are of even more relevance and assistance to stakeholders wrestling with ancillary-care responsibilities in these complex prevention trials. Because the existence of guidance may not be sufficient to achieve ethical practices, a series of recommendations for strengthening practices were also made.

One of the pitfalls of utilizing empirical data to reflect on ethical guidance is that one might, inadvertently, recommend changes to guidance that decreases protections for participants and participating communities (cf. Kon, 2009). This study recommends that ethical accounts should address certain empirically-identified concerns and complexities, highlight particular components, or incorporate additional features into their account. This study also

recommends that ethical guidelines should have expanded or additional text to better address empirically-identified complexities and to reconcile implicit approaches that may be unclear. These recommendations should, in no way, decrease protections for participants in HIV vaccine trials.

This empirical study has highlighted several concerns and complexities that provide grist for the mill for developers of ethical models and ethical guidelines to consider more fully. What do participants actually contribute? What is an appropriately 'dosed' return? How much privileging of participants in relation to others is acceptable? When have researchers done enough to help, including to engage others to help? In conjunction with improved practices, guidance that explicitly addresses these complex issues may further strengthen the ancillary-care component of such trials, contributing to their overall ethical rigor.

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## APPENDICES

### Appendix 1 Summary of recommendations in ethical guidelines

Recommendation	SA MRC (2003)	UNAIDS/WHO (2007; 2012)	UNAIDS/AVAC (2011)
PARTICIPANTS/ HIV needs	Ensure high quality treatment and care, including ART [OIs; STIs; family planning]	Provide access to treatment regimens among those internationally recognised as optimal, including ART  [Opportunistic infections, STIs, reproductive healthcare]	Ensure access to comprehensive care and ART regimens internationally recognised as optimal
PARTICIPANTS/ SRH needs	Participants should get STI treatment	Participants should get STI treatment  Provide appropriate sexual & reproductive health counselling/ services to participants	SRHC is provided as an example of non-HIV care that could be made available to participants
PARTICIPANTS/ other needs	Participants should have regular and supportive contact with healthcare workers	Participants should have regular and supportive contact with healthcare workers	Participants will have other needs;  Discuss with relevant stakeholders access to services (negotiate)

Recommendation	SA MRC (2003)	UNAIDS/WHO (2007; 2012)	UNAIDS/AVAC (2011)
VOLUNTEERS/ HIV needs	Refer to existing services	Refer to clinical and support services	Discuss access to HIV services with relevant stakeholders
VOLUNTEERS/ other needs	Specify in protocol referral processes for those excluded		
COMMUNITY needs	Build capacity of trial-linked health-care centres to deliver services to the community to improve local standard of care	Build capacity to deliver HIV services Ensure that communities have state of the art reproductive healthcare services	
Assess community health needs	Understand the health context	Assess vulnerabilities e.g. health in participating communities	
Consult with community/ stakeholders	Community participation could include input into care decisions  Community representatives should play a role in determining how capacity is built	Ensure transparent & participatory process involving all research stakeholders prior to trial.  Secure stakeholder agreement on the level, scope and duration of the HIV care package, and mechanisms  Do not proceed unless all stakeholders have reached consensus on access to care/	Discuss with relevant stakeholders HIV care (numbers, package, guidelines/laws, mechanisms) and clarify responsibilities.  Discuss with relevant stakeholders non-HIV care

Recommendation	SA MRC (2003)	UNAIDS/WHO (2007; 2012)	UNAIDS/AVAC (2011)
	Community consultation should enhance ethical soundness	treatment	
Document discussions		Document agreements about who will finance, deliver and monitor HIV care/treatment	Document discussions about HIV care, and non-HIV care
Budget	Ensure that resources are contributed towards treatment and care	Ensure appropriate financial arrangements in place to implement agreements between partners	Ensure sufficient funding/ create a budget/ allocate funds so HIV and non-HIV care can be delivered
Engage SERVICE-PROVIDERS: assess		Explore capacity to deliver HIV care and treatment services	Identify services and capacity for HIV and non-HIV care [seek views]
Engage SERVICE-PROVIDERS: build capacity	Build capacity of trial linked centres to deliver HIV services to the host community	Build local & national capacity to deliver HIV care and treatment services through strategic investment	
Engage SERVICE-PROVIDERS: collaborate		Reach agreement about who will finance, deliver HIV care/treatment  Collaborate with government to strengthen capacity to deliver HIV services. Central responsibility for delivery of services lies with local health systems	Clarify with health institutions responsibilities for financing/ delivery of services
Engage REVIEWERS		Ensure treatment, care and support for	

Recommendation	SA MRC (2003)	UNAIDS/WHO (2007; 2012)	UNAIDS/AVAC (2011)
	<p>Include expected benefits in the protocol</p> <p>[Benefits include access to HIV care, supportive contact with HCWs]</p>	<p>participants and community is reviewed.</p> <p>Include expected benefits in the protocol</p> <p>Benefits include access to access to HIV care, sexual and reproductive healthcare and contact with healthcare workers</p> <p>State the benefits of procedures required for the scientific conduct and ancillary services likely to be beneficial</p>	
Engage PARTICIPANTS	Ensure that participants understand HIV care and treatment; and other benefits	Ensure participants understand care available if they get HIV infection	<p>Include the HIV care and treatment package in consent forms for screening and enrolment</p> <p>Discuss with relevant stakeholders how to ensure individuals screened and enrolled are aware of how to access HIV care and treatment</p>
Monitor care		Document access to HIV care approach, successes and failures	Discuss how to monitor access to HIV care and treatment services
Reasons for addressing needs	Compensation for harm, beneficence, justice	Beneficence, Justice as equality, Justice as reciprocity	Beneficence

## Appendix 2 Letter of request for documents

16 July 2010

Dear site PI

Thank you for attending our consultation on 1<sup>st</sup> July 2009, or sending a site representative. As mentioned at the consultation, and in our circulated report, HAVEG has been funded by a grant from the Wellcome Trust to explore **care and prevention responsibilities** in HIV vaccine trials.

Our study aims to explore trial participants' access to care and prevention **services** such as treatment/care for HIV (and other conditions identified in trials), as well as counselling, condoms, circumcision, PrEP and treatment for Sexually Transmitted Infections. It also aims to explore **decision-making** to provide such services.

Our ultimate goal is to explore whether current ethical guidelines correspond with on-the-ground practices and anticipate actual stakeholder challenges. The study is conducted in the spirit of shared struggle towards a mutual goal of an effective prevention technology for all. Our research methods will be (1) document review (2) interviews and (3) questionnaire administration.

With this letter, **we are requesting access to site documents** that could shed light on care and prevention practices at your site. All the information you provide will be subject to the following protections:

- Neither you nor any member of your staff will be named in any public report
- Your site will not be named in any public report
- Before release of final public reports, practices at individual sites will be aggregated into a national picture
- Before release of final public reports, our results will be presented at a consultation where comments and inputs from sites will be solicited
- Only designated members of the team who have signed strict confidentiality agreements will review the documents and they will not be released or accessed by any third parties
- Trial sponsors have been advised about this project and have expressed their general support (the [anon] network and [anon] vaccine initiative)
- The study has been approved by the following Research Ethics Committees:
  - ✓ BREC at University of KwaZulu-Natal BE 241/09
  - ✓ Wits HREC (Medical) Mog1140
  - ✓ MEDUNSA MREC/P/13/2010: CR
  - ✓ University of Cape Town HREC REF 476/2009
  - ✓ Walter Sisulu (under review)

Please note that you are of course free to refuse to release documents to us. If we can review documents in advance, this may reduce time needed for interviews. If you do release documents, this does not necessarily mean you will approve of interviews being conducted at your site or that you will agree to such interviews yourself.

We may need to contact you to help us make sense of some of the documents.

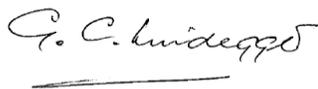
If you agree to release documents to us, the following may be helpful to our study:

- ✓ Ethics applications and protocols for HIV vaccine trials (anonymised)
- ✓ Feedback from research ethics committees
- ✓ Site/protocol specific documents regarding **care** for conditions identified in trials (such as HIV, TB, hypertension etc)
- ✓ Site/protocol specific documents regarding **prevention** practices (counselling, condoms, PEP, male circumcision, STI treatment)
- ✓ Standard operating procedures (SOPs)
- ✓ Memorandum of Agreement with referral centres
- ✓ Manual of operations
- ✓ Training materials
- ✓ Any others?

There may be other relevant documents that we have not listed above and we would be grateful for any information that, in your view, might clarify care and prevention practices at sites.

We appreciate your time and support of this project.

Yours sincerely,



Graham Lindegger (PI)



Cathy Slack Co-PI

## Appendix 3 Informed consent form

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### Information Sheet:

#### Care and prevention in HIV vaccine trials in South Africa:

#### A normative and empirical exploration

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Dear Colleague,

Hello. We are from the HIV/AIDS Vaccines Ethics Group (HAVEG), based at the University of KwaZulu-Natal. HAVEG does ethical-legal research in HIV vaccine trials. We are inviting you to participate in a study. This study will explore care and prevention in HIV vaccine trials.

#### Who funds our study?

This study is funded by the Wellcome Trust, a UK-based charity that funds health research.

#### What is the purpose of our study?

Our study will look at how researchers help HIV vaccine trial participants to avoid HIV, get care for HIV if they do get infected, or get care for other health problems. It will look at how these important decisions are made. In other words, we are exploring care and prevention **practices** at HIV vaccine sites in South Africa – delivery of services to participants and decision-making to provide services. We are interested in the challenges and successes experienced by researchers, as well as the concerns and views of other stakeholders on this issue (e.g. members of Community Advisory Boards (CAB), ethics bodies and sponsor teams). We are also interested in the views of stakeholders about **ethical standards** in recent guidelines on HIV vaccine trials.

We want to see whether what happens in practice matches what ethical guidelines say should happen. If there is not a good match, we want to understand why: for example, are ethical guidelines too difficult to implement? We also want to see if ethical guidelines help stakeholders with the actual concerns and worries they have. If guidelines don't address people's real concerns, how can they be improved? Based on the findings, we will make recommendations to strengthen care and prevention practices (including the sharing of best practices), and to make ethical guidelines clearer or stronger.

#### What inputs have sites and community representatives had into our study?

In July 2009, we met with site staff and CABs from all HIV vaccine trial sites to tell them our broad aims and get their views and concerns. We clarified that the research was part of a collaborative

effort towards a shared goal of strong care and prevention at South African sites. There seemed to be general support for the study.

### **What procedures will this study involve?**

We will conduct general interviews with some site-staff (e.g. PIs, medical officers) and some other stakeholders (e.g. CAB members, review body members, sponsors). The interviews will explore their views about the important issues in care and prevention in HIV vaccine trials, and challenges and successes. For selected site staff, we will also conduct a detailed specific interview about what is actually provided to participants at their sites and how.

We will also ask site staff and members of CABs and RECs to answer a questionnaire that explores their views of ethical guidelines for HIV vaccine trials.

Later on we may ask some stakeholders to be involved in focus groups.

As background to gathering data from people, we will also be looking at various documents. We will look at ethical guidelines to understand what is expected of researchers. Where we get permission, we will also look at documents like HIV vaccine trial protocols, standard operating procedures and training materials. We will also try to understand each site better by looking at information on their websites or public documents.

### **Why have you been chosen?**

You have been identified as someone we would like to talk to because of your work at HIV vaccine sites or your involvement in a community organisation, review body or sponsor team.

### **Do you have to take part?**

No. You can refuse to take part. Even if you agree, you can change your mind at any time. You can also refuse to take part in certain procedures or answer certain questions. You can also choose to make your answers hypothetical and not about the actual group or institution you represent.

### **What are the risks of taking part in this study?**

If you are taking part in an interview, you may feel worried to talk about care and prevention practices that are not working well in the group or institution that you are a part of. You may worry that talking about these will have negative consequences for you or your organisation. Remember that you can choose not to take part, or not to answer certain questions. You can also make your answers general and not about your actual organisation.

We will make every effort to make your responses anonymous. We will not report any names of people when writing reports. We will group together information about sites into a national 'picture' before any public release. This information will be shared with stakeholders at a national consultation before public dissemination.

We are not tasked to monitor practices. However, if you inform us of something that appears to be a serious breach of practice that poses a direct risk to the health and welfare of an actual HIV vaccine trial participant, then it seems wrong for us to do nothing. So in this event, we will discuss the issue in a confidential research meeting. We may ask you for more details. A decision may be made to contact the site Principal Investigator for clarification and remedial action if necessary. In this event you will be informed and every effort will be made to maintain your confidentiality and resolve the issue in a collegial and respectful manner. Sites may have to contact their research ethics committee and/or other institutional bodies as per their own arrangements.

If you are taking part in the questionnaire, you may worry that we are testing how much you know about ethical standards. This is not the case: rather, we hope to identify those areas where ethical standards may have to be clarified, disseminated better, or even changed.

### **What are the benefits of this study?**

There are no direct benefits to participants. It is possible that taking part in the study makes you think about the issues in a new and more helpful way, however there is no guarantee that this will happen. In the long run, we hope this research will identify (at a national level) practice areas that need strengthening as well as best practices. We also hope that recommendations for improved guidelines will make for clearer direction on this issue. A site-level report identifying issues, challenges and successes at each site will be offered to participating sites to maximize benefits to them.

### **What will happen to the data and how will confidentiality be maintained?**

In general, only research staff at HAVEG will have access to the data from this study.

If you take part in interviews, your name and other identifying details will not be stored together with any data. We hope to record your interview using a digital recorder. This recording is only for our own records, so that we can get an accurate record of what is said. We will transcribe parts of the recording.. You may refuse to be recorded if you wish. Because there are a small number of target groups, it is possible that interviewees will be identifiable through, for example, rich text quotes. Every effort will be made to make interviewees as anonymous as possible.

If you take part in the questionnaire, your name and other identifying details will not be stored together with any data.

If you take part in focus groups held later on, you will be asked not to disclose things that are discussed in the group. We can't guarantee that every focus group participant will honour this agreement, so we will ask all focus group participants to be careful about disclosing information. Focus groups may be recorded if participants agree.

The tape recordings, transcripts and questionnaire data will be stored safely, that is, in a locked cabinet, and electronic records will be password protected. All the data will be kept for 5 years then destroyed.

### **What will happen to the results?**

Results will be written into:

- A national report for discussion at a national consultation and eventual public dissemination
- Academic publications in open access journals
- Conference presentations
- Two doctoral dissertations, if post-graduate approval is received.

No participants in our study will be named in any written document and efforts will be made to prevent their personal identification. Also, every effort will also be made to avoid the identification of specific sites. Sites will not be named in written reports. Site data will be aggregated to form a national picture. However, due to the fact that there are only limited HIV vaccine trial sites in South Africa, it is conceivable that some sites may be identified. A national-level report will be developed and discussed at a national consultation. An individual report tailored to each site will be offered to each site, but not for public release.

### **What do you need to do?**

If you agree to participate in this study, we will need you to sign the informed consent form below and return it to us. We will ask you to discuss any questions you may have about the study with us.

If you are a member of a trial site, CAB, review body or sponsor team taking part in a general interview about concerns and challenges, we will need about 1 to 2 hours of time. This may be in person or over the phone.

If you are member of a trial site taking part in a specific interview about care and prevention practices we will need about 1 to 2 hours of time. This may be in person or over the telephone.

If you are a member of a trial site, CAB or REC taking part in a questionnaire about ethical standards, we will need about 30 minutes. This may be in person, over the telephone or over email. At a later stage you may be asked to participate in a follow up focus group.

Remember, even if you agree to take part in some procedures you can refuse to participate in others. **NOTE:** You may not be invited to take part in all of these procedures, because some are reserved for particular stakeholder groups.

### **Will participants in this study be paid?**

Site staff and members of CABs, review bodies and sponsor teams taking part in a *general semi-structured interview* will be offered R50.00 as payment to compensate them for their time, inconvenience and expenses. Site staff taking part in *specific interviews about care or prevention practices* will be offered R50.00 respectively. Site staff, CAB members or REC members who take part in a *questionnaire about ethical standards* will be offered R35.00. If we hold *focus groups* later on, participants will be offered R50.00. **NOTE:** You may not be asked to take part in all of these instruments, because some of the instruments are reserved for particular stakeholder groups.

### **Was this research ethically approved?**

Yes. This study has been approved by the following ethics committees:

- BREC at University of KwaZulu-Natal BE 241/09
- Wits HREC (Medical) Mog1140
- MEDUNSA MREC/P/13/2010: CR
- University of Cape Town HREC REF 476/2009
- Walter Sisulu o89/009

**Who can I contact if I have questions?**

For questions related to the study, please contact the PI who is Graham Lindegger at 033 260 6166 or [lindegger@ukzn.ac.za](mailto:lindegger@ukzn.ac.za). You may also contact the co-PI who is Catherine Slack on 033 2606166 or [slackca@ukzn.ac.za](mailto:slackca@ukzn.ac.za). For questions about ethical issues in the study, you may contact the BREC ethics committee through Ms A Marimuthu on 031 260 4769, fax 031 260 4609 or email [brec@ukzn.ac.za](mailto:brec@ukzn.ac.za). For Cape Town based participants: For questions about ethical issues in the study, you may contact the UCT HREC through Ms Lamees Emjedi on 021 406 6338 or email [Lamees.Emjedi@uct.ac.za](mailto:Lamees.Emjedi@uct.ac.za)

**DECLARATION**

Consent to take part

I, \_\_\_\_\_ (full names of participant) confirm that I understand this consent form and the nature of the study and agree to take part in:

	Insert X
The general interview on care / prevention	X
The specific interview on care / prevention (Site staff only)	
The questionnaire on ethical guidelines related to care and prevention	
The focus group	

**I understand that I can withdraw from the study/ components of the study at any time.**

**SIGNATURE OF PARTICIPANT**

**DATE**

\_\_\_\_\_

\_\_\_\_\_

Tape recording consent

I, \_\_\_\_\_ (name of participant) consent to the tape-recording of the interview or focus group.

**SIGNATURE OF PARTICIPANT**

**DATE**

\_\_\_\_\_

\_\_\_\_\_

## **Master Theme 1 RECIPROCATING, ENGAGING & BENEFITTING**

### ***SUB THEME/RECIPROCATING FOR PARTICIPANTS' CONTRIBUTIONS***

*Seeing that participants step up/ stand up/ step forward [HIV]*

*Responding to risk assumption [HIV]*

*Responding to contributing passion \* [HIV]*

*Responding to commitment \* [HIV]*

*Responding to volunteering \* [HIV]*

*Responding to effort [HIV]*

*Responding to contributing time [HIV]*

*Responding to contributing HIV status [HIV]*

*Responding to contributing bodies [HIV]*

*Responding to something [HIV]*

### ***SUB THEME/STAYING INVOLVED WITH PARTICIPANTS***

*Not abandoning/ not cutting off/ not dumping/ not dropping/ not letting out of hands [HIV]*

*Not judging [HIV]*

*Treating holistically [HIV]*

*Being involved [pregnancy]*

### ***SUB THEME/BENEFITTING & SERVING PARTICIPANTS***

*Perceiving on-site provision of contraception as better counselling and less waiting*

*Perceiving onsite treatment of STIs as more respectful counselling, less waiting, better confidentiality*

*Perceiving on-site treatment of other ailments means less waiting*

### ***SUB THEME/RESPONDING TO/ CARING FOR PATIENTS***

*Invoking clinical role [non-HIV]*

## **Master Theme 2 RECONCILING**

### **SUB THEME/ UNDERSTANDING STEPS AS 'FOR SCIENCE'**

*Understanding monitoring participants with HIV as integral to the science*

*Understanding contraceptive access as for safety*

*Understanding monitoring pregnancy outcomes as for safety*

*Understanding monitoring other conditions as adverse events management*

### **SUB THEME/ UNDERSTANDING STEPS FOR SCIENCE AS ALSO HELPING**

*Understanding that serial monitoring means early referral/ not getting lost [HIV]*

### **SUB THEME/ TAKING STEPS TO HELP**

*(see below)*

### **SUB THEME/ UNDERSTANDING HELPING STEPS AS 'SOFT SCIENCE'**

*Perceiving on-site provision of contraception as soft science/ more control, better monitoring for site*

*Perceiving on-site provision of STI treatment as soft science/ convenience, better retention/ monitoring for site*

*Perceiving on-site treatment for other ailments as soft science/ better retention, data for the site*

### **SUB THEME/ UNDERSTANDING STEPS AS FOR SCIENCE AND HELPING**

*Seeing follow-up/ monitoring of CD4/ VL as science plus ancillary reason*

*Seeing on-site provision of contraception as soft science plus ancillary reason*

*Seeing follow-up/ monitoring of pregnancy as safety plus ancillary reason*

*Seeing on-site provision of STI as soft science plus ancillary reason*

*Seeing follow-up/ monitoring other ailments as safety plus ancillary reason*

### **SUB THEME/ UNDERSTANDING STEPS FOR SCIENCE AS NOT HELPING**

*Encountering conflict/ pregnancy counselling & participant choices*

*Encountering conflict/ contraceptive counselling & participant choices*

*Encountering conflict/ disease-monitoring protocols & participant choices*

## **Master Theme 3 PRIVILEGING**

### **QUESTIONING SPECIAL TREATMENT FOR PARTICIPANTS**

*Feeling ambivalent/ unsure*

#### **ENDORISING SPECIAL TREATMENT BUT NOT AGREEING ON RESPONSE**

*Seeing that participants deserve more psychosocial support than citizens [HIV]*

*Seeing that participants deserve assisted referral [HIV]*

*Seeing that participants deserve better monitoring than citizens [HIV]*

*Seeing that participants deserve best care 'in region' [HIV]*

*Seeing that participants deserve care in 'special environments'/ faster access to ART [HIV]*

#### **WORRYING ABOUT CONSEQUENCES OF SPECIAL TREATMENT**

*Worrying about bribing/inducing/ coercing [HIV]*

#### **RECOGNISING SOME PRIVILEGING OF PARTICIPANTS OVER CITIZENS**

*Seeing that participants get closer monitoring and earlier referral than citizens [HIV]*

*Seeing that STI counselling for participants from site staff is less stigmatizing than PHC sector staff*

*Seeing that contraceptive counselling for participants from site staff is better than PHC sector staff*

#### **POSITIVE DUTY VS PRIVILEGING**

*Not declaring benefits in protocols [HIV, SRHC, other]*

*Not declaring benefits in ICFs [HIV, SRHC, other]*

#### **HELPING NON-PARTICIPANTS**

*Investing in referral sites*

*Providing services for volunteers; Providing services for citizens*

#### **TAKING STEPS THAT PRIVILEGE PARTICIPANTS ACROSS SITES**

*Seeing that referring participants to co-located care means less delay/ more stable drugs than referral to PHC*

*Seeing that referring participants to one PHC sector may differ than to another [wait times, ART-start*

*Seeing that on-site STI provision for participants means less time-wasting*

*Seeing that on-site contraception for participants means less time-wasting/ better counselling*

*Seeing that onsite treatment for participants have less time-wasting than those at PHC sector [other]*

*Endorsing variable strategies to address needs*

## **Master Theme 4 LINE-DRAWING**

### **ETHICAL REVIEW**

#### **UNDERSTANDING SOME NEEDS AS IN FOCUS**

*Understanding some needs as in 'on radar'/'related'/'looked for'/'weighed in on', 'endpoint'*

*Understanding needs in focus as deserving more demanding review steps*

#### **INVOKING COSTS**

*Time in review*

#### **QUESTIONING APPROACH/WONDERING IF MORE SHOULD BE DONE**

*Questioning approach/ not discussing substance/ not monitoring/ uneven policy*

### **ADDRESSING NEEDS**

#### **UNDERSTANDING SOME NEEDS AS IN FOCUS**

*Understanding some needs as 'outside scope'/'beyond scope'/'outside focus*

*Understanding needs in focus as deserving more demanding steps*

*Endorsing referral for non-HIV needs*

*Endorsing assisted referral for HIV*

#### **INVOKING THE PRIMARY MISSION**

*Understanding primary mission as answering the question/ looking for prevention tool/ implementing trial*

#### **INVOKING COSTLINESS OF CERTAIN RESPONSES ON PRIMARY MISSION**

*Invoking costs/ using financial resources*

*Invoking costs/ diverting staff*

*Invoking costs/ undermining science*

*Invoking costs/ shouldering legal responsibility*

*Invoking the 'reasonable' response*

#### **INVOKING RESPONSIBILITIES OF OTHERS**

*Requiring ART plans/ not monitoring*

*Relying on sites for STI and contraception/ not supplying*

**QUESTIONING APPROACH/ WONDERING IF MORE SHOULD BE DONE**

*Questioning approach/ seeing volunteers don't get CD4 and VL*

*Questioning approach/ fund for domestic participants*

*Questioning approach/ third-line regimens*

*Questioning approach/ domestic ART initiation criteria*

*Questioning approach/ diagnostic approach for STIs*

*Questioning approach/ injectable contraception*

**ENGAGING PARTICIPATING COMMUNITY**

*Seeing some stakeholders as in focus*

*Invoking primary mission*

*Invoking costs*

*Questioning approach*

## **Master Theme 5 PARTNERING**

[site-staff and participant]

### **VALUING PARTNERING**

*Seeing participant as holding power*

### **QUESTIONING IF PARTNER COULD BE DOING MORE/BETTER**

*Encouraging participants to access HIV care/ encountering denial [SS]*

*Checking participants referral preferences/ encountering disclosure fears [SS]*

*Requesting feedback from participants about off-site care/encountering inadequate reports [SS]*

[Site-staff and Service provider]

### **VALUING PARTNERING**

*Seeing as collaborators & co-contributors/ Reducing HIV*

*Recognizing distinct contribution/ Durable provider*

*Seeing relationship as organic/ constant investment*

*Seeing as exchange STI, cont, preg [Site-staff-Service provider]*

### **QUESTIONING IF PARTNER COULD BE DOING MORE**

*Seeing vested interests/ [encountering resistance to dispensing ST/ cont] [SS]*

*Seeing as resource-constrained/ time-wasting, bad STI/ cont counselling, stigmatizing attitudes [SS]*

*Feeling thwarted/ ART initiation [SS]*

*Seeing as myth-holders*

[Site-staff and network]

### **VALUING PARTNERING**

*Seeing as committed/ Recognizing HIV treatment fund*

*Recognizing distinct contribution/ local knowledge*

*Consulting investigators about care in protocol development/ recognizing expertise, local resources*

*Relying on site resources/ expertise to address SRHC [NW]*

### **QUESTIONING IF PARTNER COULD BE DOING MORE**

*Seeing vested interests/ questioning funding restrictions for STI, contraception, care [SS]*

**DOING COVERT OPERATIONS**

*Charging funder to open file to finance STI, other [SS]*

[site-staff and CAB]

**VALUING PARTNERING**

*Seeing as committed/ recognizing researcher steps for care [CAB]*

*Recognizing distinct contribution/ value of CAB's to improve implementation] [SS]*

**QUESTIONING IF PARTNER COULD BE DOING MORE/ BETTER**

*Seeing vested interests/ not accessing Ps [CAB]*

*Seeing as resource-constrained [Questioning power, representativeness] [SS, NW]*

*Worrying about unreasonable views/ questioning which views to allow [SS]*

[Site-staff and REC]

**VALUING PARTNERING**

*Seeing researchers as committed, well-established, stable, experienced [REC]*

*Seeing as collaborators/ leveraging sponsors] [SS]*

*Seeing as collaborators/ co-setting the standard] [SS]*

**QUESTIONING IF PARTNER COULD BE DOING MORE/ BETTER**

*Seeing vested interests/ 'deviation-monitors' [SS,NW]*

## **FROM MASTER THEME 1: TAKING HELPING STEPS**

### ***Taking steps to help address PARTICIPANTS HIV needs***

*Providing HIV counselling to participants on-site [SS]*

*Referring for ART to co-located PEPFAR funded clinics or public sector [SS]*

*Encouraging participants to access HIV care/ encountering denial [SS]*

*Checking participants referral preferences, choices/ encountering disclosure fears [SS]*

*Securing permission from participant to share medical information about HIV [SS]*

*Requesting feedback from participant about HIV care received at referral facilities [SS]*

*Understanding referral site functions [SS]*

*Reaching agreements with referral sites about sharing info/ seeing as reducing burden [SS]*

*Sharing letters & medical information with referral sites [SS]*

*Intervening at referral sites [SS]*

*Sourcing funding from donors for the HIV treatment fund [NW]*

*Requiring researchers to develop HIV treatment plans/ assisting with plans [NW]*

*Drafting comprehensive HIV treatment plan [ART] for the network [SS]*

*Doing helping/Facilitating ART access between sites [HIV] [NW]*

*Disseminating best practices to researchers about HIV care [NW]*

***Taking steps to help PARTICIPANTS with STI/ SRH/ other needs***

*Providing participants with STI counselling on-site [SS]*

*Addressing STI treatment for participants by onsite provision vs referral to PHC [SS]*

*Engaging service-providers to procure STI treatment/ encountering resistance [SS]*

*Addressing participants contraceptive needs by onsite provision versus referral [SS]*

*Engaging service-providers to procure contraception/ encountering resistance [SS]*

*Providing counselling about pregnancy options on site [SS]*

*Providing counselling for pregnancy options [SS]*

*Referring participants for pregnancy services [A/N or TOP] [SS]*

*Referring participants for PMTCT if pregnant and HIV-infected [SS]*

*Understanding referral resources [SS]*

*Sharing information with referral site [SS]*

*Addressing participants other needs by providing onsite treatment vs referral [SS]*

*Addressing participants other needs by referring to private care [SS]*

*Planning/ developing SOPs to address participants other needs [SS]*

*Counselling participants to access general care/ overcome denial [SS]*

*Checking participants referral preferences/ accessibility [SS]*

*Requesting feedback from participants about off-site care [SS]*

***Taking steps to help VOLUNTEERS with HIV***

*Providing volunteers with counselling on-site [post-test/ RRC] [SS]*

*Providing volunteers offers of extra support [SS]*

*Checking volunteers HIV care referral preferences [SS]*

*Referring volunteers for HIV care/ providing letters and results/ not CD4 or VL [SS]*

***Taking steps to help VOLUNTEERS with non-HIV needs***

*Providing volunteers with STI Rx onsite versus referral [SS]*

*Procuring to provide STI treatment to volunteer's onsite [SS]*

*Providing volunteers with contraception on-site versus referral [SS]*

*Procuring to provide contraception to volunteers' onsite [SS]*

*Providing pregnant volunteers with counselling [SS]*

*Referring pregnant volunteers for services [SS]*

*Addressing volunteers other needs by providing onsite treatment versus referral [SS]*

*Encouraging volunteers to access care/ overcome denial [SS]*

***Taking steps to help CITIZENS in the community***

*Providing training to public sector staff [SS]*

*Posting site staff to assist with service-delivery [SS]*

*Collaborating with PHC staff on educational events [SS]*

*Offering HIV testing to community [SS]*

*Offering other health services to community [SRH, general] [SS]*

*Undertaking prevention initiatives in community [SS] [CAB]*