5

PrEPs, Multiplicity and the Qualification of Knowledge and Ethics

Introduction

In the previous chapter, we were concerned to trace the way that PrEP as a pill, PrEP RCTs and bioethics were collectively and mutually singularized. By focusing on various entities, not least through an engagement with expert and practitioner accounts, we showed how these were enacted as quantitative objects: that is to say, they were stabilized in relation to a set of criteria, measurements, parameterizations or standards that seemingly stood 'outside' of the complex events that comprise the trialling of the PrEP pill.

The discussion was thus primarily concerned with how the event of a PrEP RCT was essentially 'closed down' (in the sense of being reified as opposed to being stopped). As we argued, this was mainly due to the role – the 'ingression' – of an externalized conception of the RCT as a technical and social gold standard. Here, we formulated the notion of trial event along four dimensions: the gold standard-ness of RCTs is a core element – prehension – present in the making or eventuation of the trial (that is, it is instrumental in the heterogeneous enactment of the trial); simultaneously, it served as an attractor toward which the trial is moving (as the meaning and practice of the RCT is oriented toward the prospect of gold standard-ness, so the openness of the trial event is in the process of closing down). These – the presence and the prospect of gold standard-ness – are the two dimensions that we concentrated upon in the previous chapter.

In this chapter, we begin to explore the way that the eventuation of PrEP RCTs is indeed open in the sense of being marked by becoming-with, and is thus generative of new potentialities. We therefore

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consider how gold standard-ness itself *emerges through* the eventuation of PrEP RCTs. That is to say, we examine how gold standard-ness in being eventuated by each trial is, also, in principle at least, open to an immanent reconfiguration: it becomes something other. The fourth dimension of the event relates to the way that gold standard-ness is also what might be called a 'provocation': it is a sort of 'anti-attractor' that orients the RCT event toward alternative prospects, precipitating 'counter-reactions' and the likely actualization of unanticipated elements of the RCT PrEP event. In the present case, this most obviously takes the form of various types of resistance to, or subversion of, the conduct of the trial but as we shall see, it can also entail a reworking of, for instance, the very idea of 'data'.

Having set out the general approach of the chapter, we should warn that, while we can analytically distinguish between these aspects of the event, in practice, these cannot always be so readily disentangled empirically.

By focusing upon this open, immanent, virtual aspect of the RCT PrEP event, we are also addressing the ways in which the pill, bioethics and the RCT are themselves fluid, multiplicitous, emergent – what we call, qualitative things.

In what follows, we expand on this at length, detailing these processes of 'qualification' in a number of analyses of PrEP RCTs and drawing again on our empirical materials. To do so, we begin by taking stock of the sheer complexity of the RCT PrEP trials. Here, our aim is to indicate how the elements that are relevant for grasping the success or otherwise of such trials (success not only in terms of assessing efficacy, but also of enabling the successful ethical and practical conduct of the trials) proliferate, seemingly endlessly. Or rather, we show how the variety of elements that emerge within and across trials challenges the very idea of 'a' PrEP pill or 'the' RCT and its gold standard status. As such, we re-consider the ways in which the RCT and its gold standard-ness emerge through the specific eventuation of trials, and across trials (where different trials are brought together to compare efficacy of PrEP across different or the same populations). We then address how the abstraction that is the gold standard-ness of RCTs 'provokes' a reaction (that is, serves as what we have called an 'anti-attractor'). It ironically enables virtual aspects of the RCT event that are otherwise marginal or 'antagonistic' to be actualized. As we shall see, and as the partial listing of the sheer complexity of the PrEP RCTs hints at, these marginal or 'antagonistic' virtualities that become actualized are 'corporeal' as well as 'social', 'microbiological' as well as 'political', 'pharmacological' as well as 'ethical'.[1]

The complexity of what comprises PrEP RCTs

In Chapters 2 and 4 we addressed the sheer complexity of PrEP RCTs not least as it manifests itself in 'offshore' trial sites. Especially in the last chapter we saw how this complexity, that is both human and nonhuman, is something that confronts trialists and practitioners who, in turn, attempt to 'domesticate' it by drawing on such skills as simplifying, disambiguating, itemizing, reducing and comparing. We distilled these various activities into a single term – quantification – which served to denote the use of external criteria in order to characterize an RCT, whether as a technical biomedical exercise or a bioethical endeavour. However, as we also documented in that chapter, these quantifying efforts bring with them their own specific and often unanticipated relations and dynamics. In this chapter, we pursue in more detail the struggles that scientists confront in facing up to this complexity – what we shall call 'qualification' – while they are simultaneously being drawn toward their standard forms of 'quantification'. Inevitably, we must focus on only a few examples of these struggles. However, in order to impress again the 'sheer complexity' of the trials, we revisit a sample of parameters and variables – or, in Whiteheadian terms, the prehensions – that go into the making of an RCT. These are taken from the descriptions of PrEP RCTs and PrEP by PrEP's various stakeholders.

The following list might be read as a partial compendium of the features of PrEP or PrEP RCTs that are understood within the HIV prevention field to present major challenges. Put another way, the events that we list below serve as a basis for the analysis of qualification that follows in the rest of the chapter insofar as they point to the possibility of an alternative eventuation of PrEP RCTs, bioethics and the pill.

Item 1: Disinhibition/Recalculation

For those conducting RCTs there is at a least partial recognition that the RCT will have complex effects upon the participants. In this sense, what is more or less tacitly envisaged is a participant who, in being-with new technologies (such as PrEP) that promise a possible reduction in their risk, may alter his/her otherwise safe sex practices (in both the placebo and a partially effective product arm) and, in turn, could be placed at increased risk of HIV infection. As a corollary with PrEP, there is also a concern that if it were to become available after the RCT it may reduce the perceived risk of HIV and lower condom use. Some individuals may assume that they or their sexual partners (if on PrEP) are sufficiently protected by PrEP. In sum, presumed changes in people's tacit risk

calculus could significantly undermine condom use not only during the RCT, but also subsequently.

Contrary to this potential for what is referred to as 'disinhibition' (see Padian et al., 2008), there is the view that, as part of the trial, the provision of 'risk reduction counselling' along with the ready availability of prevention materials such as condoms or even male circumcision, reduces risk. Ironically, this raises some consternation. The 'unfortunate' technical side-effect of achieving lower levels of infection is that the number of infections that arise in the placebo arm will be insufficient to evidence efficacy in the treatment arm (Padian et al., 2010).[2]

Item 2: Presumption of gender and economic relations of power

Initially, much of the impetus for a biomedical prevention technology came from the Global Campaign for Microbicides (GCM) set up with a feminist intention to 'empower' women by providing them with the means to protect themselves and their partners. The aim was to provide an intervention that would not require a male sexual partner's collaboration.[3] PrEP may offer women a prevention technology that they can use without letting it be known to their partner, a partner who they may suspect has had relations with other women and may be HIV positive. However, this formulation of women is based very much on a certain conception of an individual, a conception that might well be characterized as a neoliberal autonomous subject, whereas some women may not think of, or enact, themselves in this way (see, for example, Woodsong and Karim, 2005). Rather, they may regard themselves as an extension of their male partner or as a member of a kinship network whose sexual and reproductive activities are not theirs to determine (Woodsong and Karim, 2005). In various ways, then, PrEP may enter into and potentially alter gender relations. Conversely, it may be the case that such gender or kinship (or other) relations are so entrenched that PrEP becomes something other than simply a preventative intervention. For example, by ensuring 'her' health against HIV infection and illness, a woman may retain her function as the primary carer in a family unit in a manner that is possibly, although of course not necessarily, subordinate within this set of relations.

Item 3: Physical differences between men and women

Results from trials to date suggest that there may be differences between men and women, although, as we discuss later, this is a highly convoluted picture. While the efficacy of PrEP has been established in RCTs with men who have sex with men (MSM), and there is evidence from

other studies that it works in women, two large trials involving women-only participants – Fem-PrEP and VOICE discussed in Chapter 4 – have produced confounding results. At this time, the main explanation offered for disparities in results between men and women seems to be that the women participants in Fem-PrEP and VOICE have been less adherent to the dosing requirements of PrEP than in the other trials.

Item 4: Viral adaptation/waning of efficacy

One of the concerns with using antiretroviral drugs that may not give *full* protection is that a person using the drugs will become infected with HIV. In such circumstances, PrEP can be understood to morph from a prevention technology to a 'sub-optimal' therapy. The 'sub-optimal' qualifier is because, as noted briefly in Chapter 1, Tenofovir, or the combination of Tenofovir and Emtricitibane in Truvada, may not sufficiently suppress the process of viral replication during early or ongoing infection and result in the emergence of a drug resistant strain of 'the' virus (Van Damme and Szpir, 2012). In turn, this may reduce the range of treatment options and is of special concern to any country in which the drug therapy options are relatively few. A further concern is that an unknowingly newly infected person continues to take PrEP on the presumption that he or she is still HIV negative, has unprotected sex (without a condom) with a known HIV negative partner. This could lead not only to further infections but in theory at least also to infections that are potentially drug resistant (see Paxton et al., 2007:89 for an argument against this concern).

Item 5: Dosing

So far PrEP has been trialled as a pill a day intervention. It has been shown to be most efficacious when it is taken consistently on a daily basis. In the iPrEX study, infections occurred amongst those reporting inconsistent use and/or amongst those whose blood tests showed no evidence of the presence of PrEP (Grant et al., 2010). However, this account is complicated by the lack of clarity over the most suitable dosing 'tactic': thus it might be the case that taking PrEP for 24 hours, or 2 days before exposure; or immediately before and, then for a longer period after exposure, might be sufficient.

Item 6: Timeframe of trial and 'frailty'

The point of RCTs is that they generate statistical evidence of an effect. However, it is not always clear what is responsible for an effect. As noted in Chapter 4, the figures are derived at intervals that may be mapping

something more than simply the number of new infections. For instance, as we noted in reference to O'Hagan et al. (2012), the cohort in the placebo arm may be subject to a selective temporal effect whereby those participants most at risk become infected early on, while those who remain uninfected continue to be so over the subsequent course of the trial, that is, they continue to be less at risk. If this pattern occurs, then the difference between the two arms of a trial reduces over time: results that might have initially indicated an efficacious intervention in the experimental arm may come to look no different to the results in the placebo arm.

Item 7: Noncompliance

For trialists one of the important measures in a trial is dosing compliance, and increasingly blood tests are used alongside self-reporting to monitor compliance. If drug levels in the blood are found to be low, this is taken as an indication of possible poor adherence even if the self-reporting indicates otherwise. However, the practice of dosing is recognized to be somewhat contingent on other factors. For instance, the women in the FEM-PrEP trial have been reported as possibly less likely to have been compliant compared to the Partners Study because they were younger, single and believed they were subject to low risk. For the women in the Partners Study who were in a relationship with a known seropositive partner, the fact that they were in a relationship was presumed to provide the incentive to dose.

Item 8: Local government and community support

All RCTs require the agreement of the government of the country in which they are being held. Considerations over whether a RCT should take place include not only the assent of a country's relevant authorities but also an assessment by trialists of that country's resources. The assessment may extend to an evaluation of how the trial itself may contribute to capacity-building in relation to the medical infrastructure. The process of realizing a RCT is, itself, lengthy and involves numerous actors who enlist support from the community, make arrangements to provide treatment for participants who become HIV-infected during a trial, organize compensation for participants who experience trial-related adverse events, and implement informed-consent procedures (see Lagakos and Gable, 2008). Taking these points together, we can see that an RCT entails a multiplicity of practical measures that have complex ramifications for the do-ability of the trial at pragmatic, ethical and epistemic levels. Indeed, in the previous chapter it was made evident that

many actors may partake in how a trial eventuates, for example: research participants, activist groups, trial sponsors, international aid funding.

Item 9: Impact of testing for HIV infection prior to entry into a trial

Prior to the undertaking of a biomedical prevention trial for an intervention such as PrEP, it is necessary to make certain that the participants are HIV seronegative, that is, that they do not already have the virus. Because an HIV positive result is anticipated to be a major life-changing phenomenon, positive results are usually given in the context of counselling. But, as we saw in the preceding chapter, the revelation of HIV positive status has implications and impacts beyond the potential trial volunteer.

Item 10: Recruitment and retention

Recruitment and retention for HIV biomedical prevention RCTs – which may involve up to several thousand participants at one site or multiple sites – may be hampered by resource-poor settings with limited infrastructure and by highly mobile and diverse populations. Follow-up on completion of the RCT may take place over several years. If there is slow accrual or poor retention of trial participants, the trial may be underpowered or, according to the RCT framing, produce skewed results.

Item 11: Contexts of informed consent

Obtaining what is termed the informed consent of a research participant is a standard ethical requirement of biomedical research as with social research, yet continues to be recognized as problematic. In part, this is because informed consent is grounded in a culturally specific presumption of the autonomous individual – a presumption characteristic of the countries where sponsors and many principal investigators of RCTs reside – but not necessarily relevant to the locale of the RCT (see, for example, Woodsong et al., 2006; Woodsong and Karim, 2005). According to a study by Ruzario et al. (2012) female trial participants in regular heterosexual relationships differed in how they conceive their relationship to their partner. Some reported that 'he' should be involved in their decision to consent which suggests that they did not see themselves as the appropriate consenting subject. The general point is that while consent can be seen to serve as a marker of respect and agreement that simplifies involvement in the RCT for trialist and volunteer alike, in its practical negotiation and establishment, consent may generate a spectrum of issues which range from the process of explaining the trial and the presumption that prospective participants know the

right questions to ask in order to be sure of how the trial may affect them (Mahvu et al., 2012), to the cultural inappropriateness of seeking consent in communal societies in which community representatives influence decisions about participation in activities, including research projects. Along similar lines, and in keeping with the dictates of giving consent, participants may be required by a trial to engage in practices, which may be contrary to, or conflict with, local cultural norms. The example offered by Woodsong and Karim (2005:413) is that of topical microbicide research which requires women to discontinue practices such as using vaginal drying agents. Another example is the insistence that married partners use condoms.

To be sure, the issues raised in this section comprise a very partial list, as will become apparent when additional issues are addressed below. The key point is not that the PrEP RCT is a heterogeneous event of enormous complexity – that should be obvious enough. Rather, it is that this complexity enfolds a series of virtualities. In the previous chapter, we saw how these included the attractor of what we called 'gold standard-ness'. We shall see this again, but we shall now explore how trialists themselves are aware of, and grapple with, how this gold standard-ness is emergent, a matter of laborious accomplishment, a goal always already on the brink of disintegration. But further, we shall also trace how gold standard-ness can serve as an anti-attractor that lures a very different and divergent set of prospects for the trial in question.

Three eventuations of gold standard-ness

In this section we consider the ways in which gold standard-ness emerges through, rather than is 'imposed' on, the process of a trial. So, rather than see it as an 'entity' that enters the trial event, or an external standard toward which the trial event is 'attracted', we trace how it 'becomes-with' in relation to, for instance, the complex and multiple enactments of the PrEP pill, women and men as both bodies and social actors, the trial as a technical exercise, and the ethics that putatively underpin RCTs. Inevitably, these are not always easy to disentangle; however, we have organized the discussion around three broad examples that we have labelled: RCT and Methodology, Pill (Bodies and Agency), and Ethics.

RCT and methodology

In the previous chapter we examined how the PrEP RCTs were 'singularized', not least in their guise as exemplifications of a generic – gold

standard – form of testing for the efficacy of new medical interventions. We noted how external parameters of design and calculation were used in the enactment of the RCTs as a quantitative object that embodied gold standard-ness. We also mapped several of the challenges faced by various actors involved in the pursuit of gold standard-ly trials. However, we propose that the PrEP RCT can be rethought in terms of a qualitative thing which is emergent – becomes-with – in the concrete eventuation of the trial. Here the trial is not simply an event that is, primarily, clinical rather than, say, political, or economic, or cultural. Of course, scientists know full well that the trial event is all these things too. After all, they must arrange – that is, entangle themselves in – the political, economic and cultural complexities of those offshore settings in order to ensure that these trials can happen in the first place. However, these elements are usually seen as extraneous to the essence of the trial. That is, they are seen as secondary qualities to the primary ones of clinical and ethical gold standard-ness. Below, we again draw from the comprehensive guide to conducting RCTs within the HIV field edited by Lagakos and Gable (2008), in order to demonstrate how this local complexity is at once acknowledged but then addressed as a secondary quality that is 'added' to the primary quality of the rigorous – gold stardard-ly – randomized controlled trial.

We see the primary qualities set out in the following remarks:

> When planning a late-stage randomized clinical trial, investigators need to consider a number of design features, including (1) the number of subjects and duration of follow-up; (2) whether the trial will evaluate efficacy or effectiveness; (3) whether to begin with a smaller (phase 2) trial, with the understanding that a larger (phase 3) trial will follow if the results are promising…; and (4) how to choose a control group or groups. (Lagakos and Gable, 2008:69)

But these are then qualified by secondary qualities that might characterize the trials:

> A number of factors influence these choices, including the anticipated HIV incidence rate for the control group(s), the rates of product nonadherence and discontinuation owing to pregnancy and other reasons, and the rates of loss to follow-up, as well as the uncertainty surrounding these assumed rates and the resulting effect on the power of the trial. Investigators must also consider how large and long-lasting the effect of the intervention must be to be of scientific interest or public health significance. (Lagakos and Gable, 2008:69)

This complex array of contingencies, rather than being seen as integral to the trial, are factors that can be overcome such that the standardized knowledge can be sustained. This standardization is particularly prominent in a discussion of the comparability of different trial designs. Accordingly, these different designs will have the same statistical power though they will differ along a number of external parameters such as the accrual of volunteers per year, the number of years of accrual, the total participants accrued, and the duration of a trial in years (see discussion in Chapter 4). At the same time, these parameters can be realized if the complex nexus of other factors (secondary qualities) mentioned above is properly anticipated. As the text goes on to recommend:

> Investigators should take steps to develop accurate *a priori* estimates of rates of participant accrual, HIV incidence, product discontinuation, and participant retention, and incorporate those into the sample size calculations. As a guard against inaccurate estimates, investigators should consider using an 'events-driven' approach. That is, investigators would analyze study results when the prespecified number of enrolled subjects have become HIV infected, rather than at prespecified calendar times. (Lagakos and Gable, 2008:75)

However, 'to develop accurate *a priori* estimates of….' assumes two things that from our analytic perspective seem peculiar. Firstly, it seems to be assumed that the process through which it is possible 'to develop accurate *a priori* estimates of….' has no impact on the prospective volunteer populations. This is itself a matter of empirical query. More importantly, it seems to be assumed that the intervention itself does not impact upon product discontinuation, HIV incidence, participant retention and so on. Clearly, in this text there is an effort to take into account the complexity of the trial event. But rather than see the RCT as emerging from that complexity, and thus orienting one's questions to the specificity of that RCT event, there is a systematic attempt to excise this complexity so that the (gold) standardized quality of the RCT can be sustained (not least across different trial designs).

A similar pattern can be found in the following quote from a paper that traced HIV acquisition in three different groups of women:

> In this evaluation of risk factors for HIV acquisition, important differences were seen in drivers of HIV incidence at the 3 study locations. Results from this analysis imply that targeted HIV programming could have a large impact on incident HIV infection in women, and

> that the most effective approach will likely vary based on knowledge of the local situation/epidemiology. (Mavedzenge et al., 2011:98)

While this is certainly an advance insofar as a local sensibility is being advocated, it neglects the fact that the process of deriving 'risk factors' is itself partially constitutive of those factors. Thus, in asking women to report on the number of sexual partners they have had, or the incidence of sexual encounters under the influence of drugs or alcohol, it is assumed that the reporting of these will be standard across the three groups. For instance, for those groups where there were relatively low numbers of sexual partners reported, it is arguably the case that there are social norms for (let us call it) 'fidelity' part and parcel of which is the enunciation of fidelity. Conversely, where there were relatively high numbers of sexual partners, it is possible that not only is having more sexual partners accepted, so too are statements to that effect. The general point is that these groups might possibly polarize in their accounting of sexual partners – the former under-estimating, the latter over-estimating. As such, these reports are not simply representations. Even though such 'sensitive information, including sexual behavior, was collected using audio computer-assisted self-interviewing' (Mavedzenge et al., 2011:90), the presentation of such information is nevertheless performative in that it serves in the re-making of local social relations and cultural conditions. What seems to be preferable to this form of seemingly unbiased quantification (in both empirical and ontological senses) is a more extended qualitative engagement with these groups of women.

However, there are some researchers who are beginning to realize that such complexity must not be 'dealt with' (quantified) but regarded as integral to the trial or study. Below we provide an extended but particularly clear articulation of this from McGrory et al.'s report (2009) which – despite invoking, albeit with a touch of irony, a clear demarcation in the practice of laboratory science and the social (as if science is not cultural in the sense of always already bound up with the political, economic etc.) – offers an insight in the complexities of the field:

> Broadly speaking, the central message is unmistakable: In the laboratory perhaps, science can indulge its natural preferences for objectivity, political neutrality, and pristine research environments. But in the field of HIV prevention research, with its numerous sensitivities, that expectation is naïve and can invite failure. Researchers need to fully internalise that insufficient attention to political context, ethical issues, and public perception can halt a clinical trial as definitively

> and quickly as negative findings at a data safety and monitoring board review. This means that prevention researchers need to do more than nod to 'social factors'. They need to think about human, social, and political issues actively and strategically at every step of the conceptualization, design, conduct, and follow-through of trials. This is especially true in resource-constrained countries where economic disparities and complex colonial histories are involved and, even more so, when issues involving sex and gender are central.
>
> Moving beyond the basics is not easy. Securing research funding, producing credible data and negotiating peer review panels is hard enough without simultaneously introducing sociology, history, politics, and mass media management into research plans and budgets. Yet fairly or not, prevention trials seem to realistically require just that. (McGrory et al., 2009:6)

This is a promising statement because it sets the scene for an emergence of the RCT that is rather different from the standard account. Indeed, it opens up the prospect for posing more interesting questions. Rather than asking how we might estimate complicating factors in order to ensure the gold standardized power of an RCT, new questions begin to emerge such as what disciplines need to inform such a process of deriving credible and robust data. The RCT thus becomes – emerges as – an occasion for drawing together an interdisciplinary range of perspectives and procedures. In the process, gold standard-ness itself shifts from signifying a certain type of focused rigour, to addressing the production of credible and robust knowledge in highly complex trial settings.

Pill (bodies and agency)

In contrast to the last chapter's focus on accounts that enact the PrEP pill as a singularized quantitative object impacting upon the body, here we focus on the ways that scientists have attempted to grasp the way that the pill has emerged through the trial. To be sure, even as a quantitative object the pill's effects are not simple but vary across bodies. After all, that is what the various statistical tests that apply to RCTs are designed to access: variation needs to be 'dealt with' in order to establish statistical significance. In the process, measures of efficacy are set against particular external parameters that ensure the singularity of the pill. Yet, to understand the pill that enters the event of the trial in this way it is not only necessarily to neglect or downplay the pill's complicating role, but to compromise the complexity of its eventuation within the trial – a

complexity in which it is, itself, transformed through its intra-actions with other entities within the trial event.

Again, scientists certainly acknowledge this complexity, at least in part. For example, extensive empirical and analytic effort is directed to addressing how 'the' PrEP pill varies across, bodies, body states, body parts and formulations. The following quote amply attests to what elsewhere we have discussed as the ontological multiplicity of PrEP (see, for example, Rosengarten and Michael, 2009b). Although rather complex in its account, it draws attention to not only how the drugs work differently due to heterogeneous phenomena – for example, metabolics, genetics and so on – but that drug efficacy *and* modes of assessment of efficacy vary. Although all antiretroviral drugs can be visibilized in peripheral blood (for example, taken from the arm), the drug itself affects how well such blood can serve as a surrogate marker of penetration of relevant tissue (for example, the walls of the vagina). That is to say, the tracking of a drug in the body affects what that drug becomes – preventative or not:

> There could be differences in drug exposure because of genetics, there could be differences in drug exposure because of environment, because of dietary influences, or nutrition or malnutrition issues as well, so different populations could definitely have different exposures … The drug has to track from the blood – when taken orally – from the blood, through the tissues, and then into the cervico-vaginal fluid … … … … And what we found is that certain drugs concentrated in the vaginal fluid, compared to blood plasma, four, five, or six-fold higher in the vaginal fluid than in blood plasma. And other drugs were much lower in the vaginal fluid than in blood plasma – 1 percent, 10 percent of what we saw in blood plasma. So the drugs themselves, the physical chemical properties of the drugs themselves, are very different, and produce very different results, depending upon which drug you're looking at. (R11)

Yet, for all its analytic sophistication, not least the recognition that the properties of various drugs emerge differently in relation to different body locales and fluids, the emphasis remains on 'the physical chemical properties of the drugs themselves'. Drugs are thus regarded as being 'in themselves', entering into a relation of 'being with' in the event of the trial, as opposed to 'becoming with' the events in which they are a part. This is not to deny that drugs have measurable effects. The problem that is being formulated here concerns how to gather accurate measures of the concentration of the drug in cervico-vaginal fluid compared with plasma. That is to say, the problem already bears the assumption that a

measure *should* be generalizable or available to extrapolation when, at the same time, it is recognized that different drugs work differently. In other words, there is a resistance to precisely what the above account draws attention to: namely, the need to work *with* the generating of differences.

All we are doing here is insisting that the specificities of the elements that contribute to the redefinition of the trial event – a redefinition that grapples with the particularity of the PrEP pill's 'physical chemical properties' as they co-emerge with bodies that are social as well as physical. Put another way, the pill (now complexly 're-informed' in the process of its deployment in the trial) serves in the enactment of complex social boundaries and social bodies. The following extract, provides a vivid picture of this, especially in relation to the position of women:

> We're certainly in a situation in which this [PrEP] could be the ultimate female controlled method, because if it doesn't have to be applied genitally, then there shouldn't be any reason that the woman's partner would know that they're doing anything for prevention. It shouldn't in any way interfere with sexual activity. That can still go on in whatever way the couple chooses for that to go on … But for women where they may have … women in situations in which they don't feel that they have the ability to make open decisions with their partners … that we also want to be careful that it's not exploited in some way. For instance, a study of vaccine attitudes in the Dominican Republic found, when they interviewed sex workers, the female sex workers were excited about vaccine research, but they also said: 'We're concerned that if we find a safe and effective vaccine, that men will use that as a reason to … to not use condoms, and we won't be able to get them to use condoms, because they'll say, "No, you're going to get the vaccine", or "You've gotten the vaccine, and therefore I refuse to use condoms"'. And what the men said was, 'A vaccine would be great, because then I'll refuse to use condoms', and 'I can have as many partners as I want'. So you wouldn't want there to be a situation like that with PrEP either. I think that we should never assume that any of these strategies is going to be a hundred per cent safe and effective, and I think we're going to still have to find ways to protect women and men from exposures that they don't want to have. (R04)

This statement clearly evokes previous mention of 'disinhibition' – the likelihood that a prevention intervention may counteract or lessen existing preventive sexual practices so that risk of infection increases. Here, the pill be can be read as 'becoming with' human bodies and

agencies in a process of disinhibition in which it is partially effective. And yet, the more typical account enacts a 'neutral' or 'good' PrEP as subject to the vagaries of human agency, specifically, to people's incapacity to enact the pills 'correctly' (Rosengarten, 2009:9).

By contrast, we can conceptualize the eventuation of the trial in rather different terms. For instance, PrEP may indeed serve to reduce the reliance by some women on a male partner's condom use. But PrEP may also feed into men's modes of thinking and acting, which subsequently affect women becoming embodied in their own modes of thinking and acting. In some respects, this is not dissimilar to the way that the consequences of hormonal contraception are borne by women's bodies. As such, PrEP might well at once reinforce and reconfigure, local social and cultural relations typified by specific forms of sex differentiation. For instance, PrEP might address the higher risk and rates of HIV infection for women but replace these with embodied risk of drug side-effects that requires medical surveillance, manifests *actual* drug side-effects, places women under demands of dosing adherence and, depending on levels of embodied 'partial effectiveness', continues to expose women to rates of HIV (albeit that these are likely to be reduced). The broader point is that the relationship between PrEP and women is but one illustration of how PrEP comes to manifest multiple functionalities that emerge in its relations with its numerous users. As should be clear, as PrEP becomes-with, these functionalities extend well beyond the medical and the clinical frame of safe and effective HIV prevention into the diverse complexities of sociomaterial life.

In sum, the pill is embroiled in an event that overspills the confines of 'physical chemical properties' and the affected physical body states, body types and body parts that the pill is, itself, involved in demarcating (in the above case, this is the eventuation of particular embodied women). This reformulation also reconfigures the pill as an object of expectation and a marker of future events. The expectation is not about refining an account of its effects in order to effect its refinement, that is, finding solutions for its efficacious operation. It is not in an event of being-with in which the pill combines with bodies while each retain their identities (as measured against external parameters). Rather, the pill is a qualitative thing emerging *with* its parameters, its bodies and their parameters (which now, as we have seen, incorporate the social dynamics of gendering).

If what PrEP 'is' emerges in complex ways within individual RCTs, when RCTs are taken together this complexity reaches dizzying heights. We return to the series of studies discussed in Chapter 4 and retrace a

sequence of reports about various RCTs, each report documenting more or less dramatic differences in results, and more or less divergent explanations for those differences. By revisiting some of the RCT findings, we see how readily an explanation is sought in a bifurcated notion of 'woman' that maps onto the biological or 'body' versus the social or behavioural 'subject' distinction. Eventuated through this is a body that is too complex or a subject that is overly recalcitrant – both of which are the undoing of what would otherwise, seemingly, be a singular efficacious pill-object.

To recall, reported findings from PrEP RCTs in 2011 and 2012 provided divergent results in relation to women. Not surprisingly, the data from the RCTs involving women was scrutinized for a causal explanation for the failure to show efficacy. As we have already noted in Chapter 4, reports from the Fem-PrEP RCT sponsor, FHI (Family Health International), have suggested that the women may have practised poor dosing adherence (in contrast with men who have sex with men) or there may be an actual lack of effect of the product among women. Poor dosing adherence was the most favoured explanation on the basis that biochemical evidence showed that the drugs in PrEP do penetrate the female genital tract, that is, that they can work in women. This was underlined by evidence from the Partner's study (and a smaller RCT in Botswana).[4] However if, as analyses of drug levels in the blood of the women suggest, the women were not taking the pill as required, and equal numbers as those in the placebo arm became HIV infected, then this would seem to point to a more important consideration. Rather than seek a causal explanation for the absence of drug efficacy which diverts attention from the long-term goal of achieving HIV prevention, it seems crucial that some attempt be made to better understand the complex relations that were eventuated in this trial, relations that might well extend far beyond the limits of this particular trial. Additionally, as we mentioned above, it was also reported that there was an 'unexpected' higher number of pregnancies in the Truvada arm compared to the placebo arm in the Fem-PrEP trial.[5] Commentaries on the trial have not focused on the possible significance of this co-affective and possibly risk-enhancing dimension to HIV risk in women (Gray et al., 2005). Moreover they have failed to fully reflect on the possible differential ways in which pregnancy, contraception, HIV infection, 'poor' and 'good' adherence co-emerge along with differential understandings about, and negotiations of, risk of infection, and risk of, or desire for, pregnancy.

Despite the important need to better understand and, indeed, conceptualize what took place, as we have noted so far the explanation most frequently offered is that women in the FEM-PrEP trial were less adherent.

This amounted to an explanation in terms of a failure on the part of the women in the Fem-PrEP trial. This was made especially clear in an article 'A tale of two trials: how adherence is everything in PrEP':

> Participants in the [the Fem-PrEP] study said they took their pills 95 percent of the time and adherence as measured by pill count was 85 percent. However when drug levels of tenofovir and FTC were measured in the blood of women assigned to Truvada, the investigators found that less than 50 percent of the women who should have been taking the drug had actually done so in the last 12 days, and less than 40 percent within the last 48 hours. (AIDSMAP, 2012)

However the article also offers a glimpse of other factors. It states that both the Partners PrEP Study and Fem-PrEP found the only side-effect that was measurably different between drug and placebo was nausea and vomiting but notes:

> In Partners PrEP Truvada was associated with a modest increase in gastro-intestinal symptoms in the first month and in FEM-PrEP the rates were also significantly higher. Whether this is enough to deter participants from continuing their pills who are not strongly motivated needs further research. (AIDSMAP, 2012)

As mentioned above, the visceral and social 'prominence' of these side-effects might be shaped by the extent to which participants are 'strongly motivated' to continue with PrEP. This becomes clearer when, later in the same article, the question of differences in adherence is addressed by the respective Principal Investigators of the Partners PrEP and Fem-PrEP trials, one trial which displayed high adherence to PrEP use and one that did not. Jared Baeten, Principal Investigator for Partners PrEP is reported as stating that the men and women in the Partners Study defined themselves as being in a stable relationship and that partners would have encouraged the trial participants to take their pills. A qualitative study is noted by Baeten to have confirmed that 'many participants saw PrEP as an opportunity to preserve their relationship despite the strain imposed by different HIV status.' In contrast, we learn from Lut Van Damme, Principal Investigator of Fem-PrEP that Fem-PrEP enrolled a cohort of women who were much younger than the women enrolled to the other studies (including Partners PrEP but also VOICE); and these younger women were also known to have relatively high levels of sexually transmitted infections. She is quoted as stating:

> Initial qualitative surveys had shown that many did not believe themselves to be at high risk of HIV, despite high incidence in their community. There was also a high pregnancy rate in the study despite reported high levels of oral contraceptive use, showing that low adherence to medications was not restricted to Truvada. There was no evidence that participants were sharing their pills with others and, contrary to what the data initially suggested, the pregnancy rate was no higher in women taking PrEP, ruling out theories that interactions between the PrEP drugs and the menstrual cycle may have made women more vulnerable to HIV. (AIDSMAP, 2012)

So, although the complexity of adherence is partially addressed in the above statements, it tends to remain an external parameter of the trial. This is made especially apparent at the close of the article by Sharon Hillier of MTN (Microbicides Trial Network): 'PrEP is very, very effective if you use it very, very well.'

In all, the approach to PrEP is somewhat reminiscent of Wynne's (1989) analysis of the expert authorities accounting for the toxicological impact of pesticides amongst farm workers: as long as the instructions were followed, then there was no risk. Wynne suggests that this reflects a sociological naiveté in relation to the complex conditions to be found on a farm where 'following the instructions' is not always practicable. At a meta-level, this is of course sociologically sophisticated insofar as it transfers responsibility from manufacturers to users. Adherence to dosing in women volunteers, or adherence to instructions in farm workers, remain external parameters that can be interjected into an event rather than seen to be emergent from the event itself where 'adherence' is less a problem in need of a solution, and more a lure for creatively rethinking the 'nature' of the trial or farming event.

Specifically, our point is that adherence emerges in the confluence and co-emergence of PrEP, bodies and agency in the specific eventuation of the trials. In the Partners trial, PrEP comprises an additional mediator through which to sustain relationships within HIV status divergent couples. PrEP is another relationality – that is, a resource – that enables the exercise of particular sorts of agency and the enactment of particular sorts of bodies within the eventuation of particular fraught sexual relationships. By contrast, in the Fem-PrEP trial, PrEP becomes a different sort of resource. Contrary to the statement above that participants 'did not believe themselves to be at high risk of HIV', the observation that the taking of contraceptive pills was lax, suggests a culture in which sexual practices entailed comparatively high risk-taking or

risk-indifference. PrEP is thus not subject to non-adherence, but becomes a resource for the continued enactment of particular 'risky' bodies and selves. The corollary notions of adherence and non adherence – while they can afford some access the heterogeneity and complexity of populations – do not address how an intervention such as PrEP becomes-with in the specific eventuations of the trial (nor how the RCT itself is transformed). On this score, in both the Fem-PrEP and Partners RCTs, PrEP has indeed been used, as Hillier put it in the quote above, 'very, very well' though to the rather different ends of eventuating widely divergent sociomaterial relationships.

Ethics

In the previous chapter, we considered the ways in which ethics were subject to gold standard-ness. We noted how external criteria were mobilized in the form of the two ethicalities of RCTs, a technical ethicality in which the trials must be designed in such a way as to make them valuable for the larger at-risk population, and a local or social ethicality where the rights of local volunteer population were upheld. We argued that these are not always consonant. In the present chapter, we begin to trace how researchers are grappling with the complexity of these ethics and, in particular, with how these ethics can be treated as emergent or 'becoming-with' in the eventuation of trials. However, as we simply mention, and elaborate in the next, this entails what we might call topological relationalities.

Our first example is a WHO/UNAIDS (2004) report '*Treating people with intercurrent infection in HIV prevention trials*' in which the provision of antiretroviral drugs for people who seroconvert over the course of a trial was justified on the basis that 'the occurrence of HIV infection is required in order to demonstrate the efficacy of the prevention intervention' (WHO/UNAIDS, 2004:4). Later, the report complicates this commitment by raising a series of questions about, for instance, what level of care should be provided (care equivalent to that available at the trial location, or in sponsor country medicine – these are often vastly different), who is responsible, and whether a partner should receive antiretrovirals at levels comparable with those who were enrolled in the trial (2004:4). Ultimately, we are left with a sense that, although the moral commitment to trial participants is clearly evident, the complex practicalities prevent the aim of an internationally standardized ethical commitment from being realized. In sum, it seems that scientific researchers find themselves facing what may appear as an ethical quandary in which

they must collectively struggle to know how to act ethically in a setting marked by asymmetrical relations between researchers and volunteers, and the local poverty of clinical resources.

This ethical quandary is further complicated by the implications of this contrast between what is medically available in the home country of the sponsors and the lead researchers, and relatively impoverished provision available to trial participants in a developing country. That is to say, trial-incurred needs (for example, HIV infection developed in the course of participating in an RCT) may place yet more pressure on what are already inadequate or stretched familial, local and national resources. Perhaps most indicative of how the vulnerability important to HIV RCTs may be compounded is the issue of 'disinhibition' mentioned at several points above. As we have noted, a trial bearing the promise of an effective intervention has the potential to lead to more unsafe practice resulting in increases in infection (AVAC, 2008). The unhappy irony is that this reinforces the impoverished conditions associated with HIV vulnerability, which also reinforces that site's suitability for RCTs. The tragedy is that this could mean an increase in the number of people with infections, people who have limited or no access to the drugs for treatment.

So, although increasingly researchers are committed to ensuring the provision of antiretroviral access (and this commitment is made more possible as treatment access improves in middle and some low income countries), international agencies such as WHO and UNAIDS have demonstrated, at best, ambivalence toward researchers' immediate obligations of care to their research subjects. The ambivalence is compounded by the way that bioethics entails the externalization of much of what is involved in the day-to-day lives of the participants. It is first and foremost concerned with such issues as participant consent, the weighing of benefit over risk, and reciprocity in the form of later access to the intervention under trial. Even, where the bioethical horizon is expanded in relation to a specific trial site or a particular sample of participants, this can nevertheless be treated by trialists as a problem for the conduct of a trial. Let us return to a quote (referred to in Chapter 4) from a leading (publicly funded) scientist writing on the problematics of providing trial participants with the best standard of prevention:

> *To comply with ethical guidelines, we have reduced our ability to assess new prevention methods* [our emphasis] by comparing them to the best available prevention standards of care (for example, limitless sexually transmitted infection treatment; frequent, individualised, and expensive

> condom counselling). Such strategies are not representative of the standard of typical prevention services in the community and are not sustainable after completion of the trial. (Padian et al., 2008:593)

As noted above, it is apparent in this statement that ethics are seen as a potential hindrance to accomplishing a statistically significant outcome through the achievement of a sufficiently substantial number of HIV infections. It is also apparent that prevention counselling, referred to as 'expensive', is an obstruction to the gold standard of the trial. But even more thought-provoking is the way in which the ethicality of an RCT should be judged against the (typically impoverished) local prevention services as opposed to those that exist in the trial's sponsoring country. In other words, the ethical guidelines enacted in the context of an 'offshore trial' are seen as over-constraining because they are likely to limit infections due to comprehensive prevention counselling, provision of condoms and possibly treatment of sexually transmitted infections that may enhance HIV vulnerability.

Padian et al.'s (2008) concern that such services are not sustainable after the RCT, underscores the difference between the country of the trial sponsor and the location of the 'offshore' trial. Indeed, as we have remarked, it is this difference in prevention standards of care that makes the 'offshore' trial location attractive. There is, in sum, a privileging of the goal of achieving a biomedical prevention technology over the goal of prevention *per se*. This can also be re-framed in terms of dual local and scientific ethicalities: local ethics that yield benefits to trial participants are a cost to the sponsoring biomedical institutions who, were they to financially support treatment after the trial, would have fewer resources to devote to RCTs elsewhere.

So, in the commentaries of UNAIDS and Padian et al. (2011) there are at once hints of an acknowledgement of, but also a withdrawal from, the complexities of bioethics as enacted in relation to PrEP RCTs. For instance, Padian et al. suggest an alternative design – a 'stepped wedge randomised trial design' – where the intervention is rolled out to participants (whether individuals or groups) sequentially, that is over a series of time periods. They go on to explain:

> The fundamental premise underlying randomized approaches to implementation is to concentrate implementation in a few sites (preferably selected randomly) and then to phase in other sites over time (for example, a 'stepped wedge'). This approach is in contrast to simultaneous implementation across many sites and districts and

> capitalizes on the logistic and fiscal realities that usually make a widespread simultaneous implementation approach difficult. Because study locations are randomized based on time, sites that at first do not receive the program initially serve as a comparison; however, all eligible sites eventually receive the program, ensuring equity. (2011:201)

Now, this might be a technical solution to the ethical issues that arise with the use of a parallel placebo arm for an intervention that is regarded beneficial. Eventually all participants receive the intervention. But, again, there is an application of external parameters here. Although so far we have focussed on 'offshore trials' in low and middle income countries with limited resources, a curious ethical dilemma emerges by setting up a control group 'in waiting'. If, for instance, an individual in the control group believes s/he has been exposed to the virus, a question arises over whether this individual should have immediate access to PEP (post-exposure prophylaxis). If the country context is such that the PEP is already available then it cannot be refused and must be considered part of the trial's standard of care. However, if the country locale does not already make PEP available, should individuals in the control group who report likely exposure to HIV within the estimated window period for PEP to be effective (within 72 hours of exposure) be prescribed PrEP drugs as a form of PEP? Given the drugs are understood as likely but not guaranteed to prevent infection after exposure, it could be argued that by not offering them, the trialists are prioritizing the conditions of the trial not the 'needs' of the individual.

Throughout our discussion we have sought to recognize the efforts made to grapple with the ethical complexities of RCTs, while also showing that in these efforts there seems to be a recourse to forms of standardization that are, ironically, generative of new problems. Having noted this, we now turn to an example where the heterogeneous complexities of a trial event are addressed in detail. Again, we return to an example mentioned in Chapter 4, the trial of PrEP amongst Injection Drug Users (IDU) in Bangkok sponsored by the US Centers for Disease Control and Prevention (CDC) and conducted in partnership with the Thailand Ministry of Public Health and Gilead Sciences who provided pharmaceutical support. Here we consider a letter published on the internet by a range of NGOs, such as the Thai AIDS Treatment Action Group (TTAG), the Thai Drug Users' Network (TDN), the Thai NGO Coalition on AIDS (TNCA), and the Center for AIDS Rights (CAR) that was sent to the key medical actors responsible for the trial (TTAG et al., 2004).

While the letter expresses general support for the 'Study of the Safety and Efficacy of Daily Tenofovir to Prevent HIV Infection Among Injection Drug Users in Bangkok, Thailand' a nexus of ethical concerns is raised. This includes the fact that no clean needles and syringes would be provided by the RCT (which as the best means of preventing HIV spread amongst IDU, would parallel the provision of condoms for trials focused on the sexual transmission of HIV). The authors note that this is particularly ethically problematic because the control arm involves a placebo. Moreover, they note that this target group is highly susceptible to local Thai government victimization as well as being deprived of what elsewhere would be considered basic facilities and resources. As the authors of the letter put it:

> We are concerned you have chosen a highly underserved, criminalized, and exploited group whose safety and best interests you are not in a position to protect, as required by the Declaration of Helsinki and other international ethical standards.

These difficulties faced by the trial scientists – who, it is claimed are not in a position to protect their research subjects – extended, and continues to extend, beyond ensuring the 'quality of referrals, support, treatment and care that the trial participants will receive'. Besides the overt violence against injecting drug users, it was noted that ensuring participant consent has been freely given would be difficult. Volunteers recruited from methadone clinics could, the letter went on to state: 'feel coerced into enrolling in your trial if they feel the services they receive may otherwise be compromised'.

These concerns, along with other criticisms, point to the design of this PrEP RCT as ethically deeply flawed. The flaw is further contextualized or, perhaps more aptly, inscribed in relation to a 'deepest concern … that no IDU or AIDS NGO community representatives have been involved from the outset on any official committee to discuss all aspects of the trial', not least before it has reached the upstream ethical committee stage. Although later a consultation process did take place, as we write, the design issues of the trial raised in the letter continue to apply. The critical commentary in the letter suggests that the ethicality of the trial should have been realized across different actors; most obviously, in relation to the letter, these actors would minimally include the trial scientists, volunteers' NGO representatives *and* new needles and syringes.

So, although the controversy surrounding these early PrEP RCTs can readily be seen to be well-founded, we see the articulation falls short of an effective challenge to the problematic nature of the RCT. What is

proposed by those objecting to the RCTs is that an ethics appropriate to a particular event needs to draw on those various actors who have a direct investment or interest in that event. However, it can be argued that the international HIV research community believes it has solved the ethical problem of RCTs by providing guidelines for volunteer community participation. Not long after the international consultations by IAS and by UNAIDS, that aimed to account for the controversy in Cambodian and Cameroon and over Bangkok trial with injecting drug users, UNAIDS commissioned AVAC to prepare guidelines for undertaking biomedical HIV prevention trials entitled 'Good Participatory Practice' (2011). The document is rigorous in its attempt to ensure that a broad group of stakeholders and, most notably, affected HIV communities in low and middle income countries targeted for HIV RCTs, have a say in identifying areas of concern. Moreover, the report argues that RCTs be adequately resourced to take into account, and where possible to address, such concerns. As an illustration of this approach to ensuring ethical RCTs, we cite one pertinent section of the report:

> Community stakeholders can provide the best information on how to design socially and culturally acceptable strategies for recruitment, screening, enrolment, follow-up, and exit. Community stakeholders included in the process of developing these strategies can play an important role in identifying and mitigating trial-related stigma, misconceptions, or miscommunication. (2011:59)

In the present case, by pulling in a variety of actors, and even when drawing upon globalizing (see Chapter 6) ethical and moral principles such as those embodied in the Declaration of Helsinki, and affirmed by the World Medical Association and by the authors of the above cited letter, it is presumed that an ethics better suited to the specificity of the trial might emerge. However – and not withstanding our note that the opposition to the RCT was insufficient to bring about a thorough interrogation – even if it is unclear how exactly this might take place, the RCT now emerges as an occasion for thinking about who can have voice in the design of a trial. Indeed, it would even appear that there are hints here of an emerging shift in what the gold standard-ness of an RCT can be (see below).

RCT as 'anti-attractor': The prospect of something other

In this section we turn to address how trials are also events which are generative of the unexpected and the novel. That is to say, over and

above the ways in which the processuality of the trial means that the RCT emerges shorn of its standard 'gold standard-ness', we explore how the openness of the trial points to a prospect or virtuality in which the event becomes something other than an RCT, or even a trial. As such, we can suggest that the abstraction of gold standard-ness serves as a sort of 'anti-attractor' that 'repels' the event toward other attractors (or external objects), which the event might take in (prehend) – attractors which might embody different ethical, political or epistemic framings.

We will begin with the example of the early PrEP trials and the controversy that arose with them. We follow by revisiting some of the material presented above with a view to deriving hints of the RCTs' potentially emerging prospects.

As we discussed in Chapter 4, the early PrEP trials generated considerable opposition. This opposition was expressed through protests both at the July 2004 XV International AIDS Society Conference in Bangkok attended by over 12,000 delegates, and in the countries where the trials were to be undertaken. The protest at the AIDS Conference attracted international media attention, particularly because of the manner in which it was staged, outside the booth of Gilead Sciences which produces the drugs used in PrEP, (Mills et al., 2005; Singh and Mills, 2005). Placards proclaimed 'Sex workers infected by Gilead'. The aim was to make it known to the conference that 960 Cambodian female sex workers were to be used as experimental subjects for PrEP RCTs. There were also protests held in Cambodia. The claims at the core of the protest were that the trial failed to provide sufficient translated information, and that care for those injured through adverse events (including provision of ARVs for those who became HIV infected while enrolled in the trial) was uncertain. Amongst the material issued by the activist groups was the following statement by Yunang Soma, head of Cambodian sex workers union:

> If they [the trial organisers] are so sure this drug is safe why don't they send their own sisters and daughters to test it? They have a lot more money than sex workers and have protection if the drug makes them sick. Also if it was their sisters and daughters they would be a lot more honest about the risks and side effects. (WNU, 2004)[6]

Now, it is certainly possible to counter the protestors' claims as being misinformed, that their arguments were based on incorrect reports in the media (Mills et al., 2005:4). For instance, it turned out that the pharmaceutical manufacturer, Gilead Sciences, was not actually directly involved in the trials and simply provided the drugs and placebo for all

PrEP trials at cost; information materials were translated into the Khmer language; and an independent data safety monitoring board, with representation from Cambodia as well as from the NIH (US National Institutes of Health), would have regularly monitored the safety data accumulated over the course of the trial (Page-Shafer et al., 2005:1501). So, even if in its specificities the protestors' statements were inaccurate and unfair, they nevertheless point to the ways in which a form of singularized bioethics focused on quantitative ethical objects, along with the quantitative objects mobilized by the RCTs and PrEP enact a particular, delimited version of the event of the trial.

The statement by Soma for WNU, quoted above, can be read as evoking the sort of uneasiness felt by many laypeople and local communities faced with the operations of biomedicine (or of technoscience more generally). Here, the form, as much as the content, of expert pronouncements (that is, the apparent certainty of expert statements) is often at odds with the contingencies experienced or perceived by local people (see, for example, Wynne, 1996; Irwin, 1996; Irwin and Michael, 2003). More specifically in the present context, it points to the asymmetrical global circumstances that underpin 'offshore trials' and the local exigencies faced by their experimental subjects. As Petryna (2007) notes in a discussion of commercial pharmaceutical research, the local desire for otherwise unavailable medicines and care may result in trials gaining government acceptance even though regulatory processes are uncertain.

Beyond this, the event of the trial becomes an agonistic occasion: a different framing of bioethics emerges. Instead of accompanying RCTs as they travel the world, serially assessing and ensuring their (demarcated) ethical status, bioethics could attend to the very process of travel. As such bioethics rather than 'solving' the particular ethical issues that arise with particular RCTs, becomes generative of more interesting problems: wrested from the hands of a professional elite, it can, for illustration, pose questions about the ethical status of offshore-ness in its various manifestations, or whether the resources that flow into the enterprise of RCTs are better routed toward lower tech, higher reliability, potentially more effective, interventions (such as the provision of condoms or clean needles). Here a different attractor comes into view – one focused less on the trialling of a drug, and more concerned with the immediate exigencies of at-risk communities.

Let us revisit the protest mentioned above, and take this together with the discussion in the 'Ethics' section of this chapter. We can re-consider those protests and proposals, and especially activist (and practitioner) recommendations for volunteer community participation. These can be

placed in relation to recent ways of thinking about the heterogeneous processes by which scientific knowledge is generated. Increasingly, many types of scientific knowledge are regarded as complex, uncertain and contingent insofar as they necessarily entail social dimensions: social activity might be part of the phenomenon under study or social elements impact crucially on the measurement and modelling of the phenomena in question (for example, global climate change and its modelling or, in the present case, the rate of HIV infection). Accordingly, the knowledge produced by this post-normal (Funtowitz and Ravetz, 1993) or Mode II (Nowotny et al., 2001) science can no longer remain the preserve of scientific institutions alone. The voice of lay or public actors is increasingly seen to be vital to the production of robust scientific knowledge and numerous authors have attempted to develop mechanisms by which lay public participation can be enabled. Promising candidates for addressing such processes of engagement include, for example, Callon et al.'s (2001) notion of hybrid forums, or Stengers' (2005) concept of cosmopolitics, or Irwin and Michael's (2003) analysis of ethno-epistemic assemblages. Crucially, in all three cases, there is an attempt to conceptualize how in the encounter between various actors that might include both 'expert' and 'lay' drawn from scientific, ethical, economic or community domains, there is a prospect of becoming-with wherein the identities of the various participants shift in relation to one another. As this happens, then the issue at stake also potentially changes as the participants who have entered into the process have themselves changed and what once was central or definitive now no longer appears so, and is replaced by a reformulation of that issue – a reformulation that might also entail inventive problem-making.

Following on from the above, we can apply this sensibility to the proposal set out in the letter regarding the CDC IDU trial in Bangkok and to the recommendations of community involvement made by the HIV community. To be sure these are to be welcomed; however, we also need to ask the extent to which such 'events of discussion' can indeed incorporate 'becoming-with' in the sense that there is a possibility of mutual change between both trial scientists and community representatives and members (who, as we have seen, do not always get it 'technically right'). The 'attractor' for the trial event now concerns, amongst other things, the nature of heterogeneous and open decision-making. To re-pose the question of the trial in an interesting way is to address the circumstances under which sponsors, scientists, activists and volunteers can all mutually change – become-with – in the process of determining whether and how an interesting and relevant event – which may incorporate a trial – proceeds.

Even so, this needs to be complexified still further. Above, we noted that McGrory et al. (2009) argue for a heightened interdisciplinarity to deal with the enormous complexities of running offshore RCTs. And yet, we might also ask what does this do to trials themselves? For instance, we can pose the following question. Within such trial eventuations, what comprises 'data', let alone credible data, when one thinks 'about human, social, and political issues actively and strategically at every step of the conceptualization, design, conduct, and follow-through of trials' as McGrory et al. (2009:6) put it? And we can also ask: What constitutes evidence of efficacy and effectiveness when, to quote McGrory et al. (2009:6) again 'sociology, history, politics, and mass media management into research plans and budgets'? These seem to us to be the more interesting questions that can be asked about the nature of trials – or rather a new attractor emerges in relation to the trial, one for which 'data' becomes an altogether more complex, heterogeneous and variegated category. This maps onto the previous discussion of the politics of bringing together different actors in the eventuation of trials, for this also raises the issue that what can count as 'data' or 'evidence of effectiveness' is now something that is open to on-going heterogeneous negotiation. We shall return to this issue in Chapter 7 where we discuss how we might engage with becoming-with and the virtual in relation to the design and conduct of RCTs.

Finally, if we reconsider the section on Pill (Bodies and Agency), we can see how the RCT and PrEP together emerge not as an occasion for adherence, non-adherence, or disinhibition, but in an eventuation in which are enacted particular more or less locally responsible bodies and agencies (even if that responsibility to particular local cultural and social expectations entail medical risk-taking). Here, there emerges another prospective attractor – one where the complex 'intra-actions' of the nonhuman (specifically the PrEP pill) is taken into account. Rather than a mere neutral 'intermediary' that is inserted into the design of the trial, it co-emerges as something different along with those who use it – trial participants and practitioners alike.

Drawing on Stengers (2010), the PrEP pill can be said to speak through different spokespersons in a range of voices: minimally, trial participant, scientific and experiential. Such diversity understandably generates all sorts of uncertainties in the process of negotiating the nature of the event – an event that, as we hinted above, might well turn out to be something other than what is typically recognizable as an RCT. If we were to use the language of the gold standard, we would say that the gold standard – as an anti-attractor – applies less to the technics and ethics of an RCT, and more to mechanisms through which is enabled an

open negotiation of what a PrEP trial event 'is'. Along the way, what is to count as 'data' is likely to be radically transformed as the problem for which data is derived, itself, markedly shifts.

Concluding remarks

In this chapter we have attempted to 'open up' the PrEP RCT and the PrEP pill by revisiting the complexities, heterogeneity and multiplicity enacted through the trials. Along the way, we have focused especially on the struggles faced by trialists (as well as activists and volunteers) as they have endeavoured to deal with these. This allowed us to begin to unravel how the gold standard-ness of the trials is eventuated both in practice and as a virtuality (an anti-attractor), and can thus become something other. If this sounds rather too vague, it is a partial upshot of our attempt to retain this sense of openness, to avoid specifying or, worse, prescribing an alternative virtuality. That will be up to the actors actually involved.

However, having made this point, we are not satisfied with simply pointing to a sensibility that engages with the virtual. We also want to 'resource' this virtuality concretely – to make suggestions about this virtuality and how it might be generative of new avenues of research and intervention. We do not view this initiative in relation to the clinical trials alone; rather, it is indissoluble from thinking about the virtualities of our own social scientific methodological and analytic practice. Indeed, here, the division between the conduct of the trials and their social scientific analysis can blur creatively. In Chapter 7 we address just this potentiality, discussing one possible route for the enactment of openness and the creative re-invention of the problem of PrEP RCTs and their objects, subjects and data. Before that, however, we want to embed the event of PrEP RCTs in relation to other events, more or less distant; or, put another way, we want to explore some of the possibly unexpected elements (prehensions) that – topologically – enter into the event of the PrEP RCT.