Published in final edited form as:

Soc Sci Med. 2013 October ; 94: 115–123. doi:10.1016/j.socscimed.2013.03.020.

Study designs for identifying risk compensation behavior among users of biomedical HIV prevention technologies: Balancing methodological rigor and research ethics

Kristen Underhill, D.Phil., J.D.

Associate Research Scholar, Yale Center for Interdisciplinary Research on AIDS / Yale Law School, Yale University

Abstract

The growing evidence base for biomedical HIV prevention interventions – such as oral pre-exposure prophylaxis, microbicides, male circumcision, treatment as prevention, and eventually prevention vaccines – has given rise to concerns about the ways in which users of these biomedical products may adjust their HIV risk behaviors based on the perception that they are prevented from infection. Known as risk compensation, this behavioral adjustment draws on the theory of “risk homeostasis,” which has previously been applied to phenomena as diverse as Lyme disease vaccination, insurance mandates, and automobile safety. Little rigorous evidence exists to answer risk compensation concerns in the biomedical HIV prevention literature, in part because the field has not systematically evaluated the study designs available for testing these behaviors. The goals of this Commentary are to explain the origins of risk compensation behavior in risk homeostasis theory, to reframe risk compensation as a testable response to the perception of reduced risk, and to assess the methodological rigor and ethical justification of study designs aiming to isolate risk compensation responses. Although the most rigorous methodological designs for assessing risk compensation behavior may be unavailable due to ethical flaws, several strategies can help investigators identify potential risk compensation behavior during Phase II, Phase III, and Phase IV testing of new technologies. Where concerns arise regarding risk compensation behavior, empirical evidence about the incidence, types, and extent of these behavioral changes can illuminate opportunities to better support the users of new HIV prevention strategies. This Commentary concludes by suggesting a new way to conceptualize risk compensation behavior in the HIV prevention context.

Keywords

risk compensation; risk homeostasis; behavioral disinhibition; condom migration; placebo-controlled trial; study design; HIV prevention; research ethics

Introduction

Recent advances in biomedical HIV prevention science have galvanized the HIV/AIDS field, generating enthusiasm for combination prevention approaches, treatment as prevention, and the expansion of prevention services to groups in which behavioral interventions have had limited effect. In several short years, HIV prevention technologies have expanded to include an efficacious vaginal microbicide (Abdool Karim et al., 2010) oral antiretroviral pre-exposure prophylaxis (PrEP) (Baeten et al., 2012; R. M. Grant et al., 2010; Thigpen et al., 2012), the first indication of an efficacious vaccine (Rerks-Ngarm et al., 2009), and firm evidence for the effectiveness of antiretroviral treatment as prevention (Cohen et al., 2011). Alongside these advances, however, has emerged uncertainty about the behavioral impacts of new prevention technologies, which will mediate the effects of biomedical prevention outside trial settings. Uptake of new technologies and adherence to dosing regimens will be important factors in real-world effectiveness, but this Commentary is concerned primarily with risk compensation behavior—a cognitive-behavioral process by which individuals may take more behavioral risks based on the belief that they are protected from adverse consequences (Eaton & Kalichman, 2007; Hogben & Liddon, 2008).

Many have expressed the concern that users of biomedical prevention technologies will expect to be protected from HIV, and will then respond by taking more behavioral risks (e.g., reducing condom use, increasing numbers of partners) (Eaton & Kalichman, 2007). These concerns have also found their way into regulatory processes; for example, risk compensation questions played a role in discussions about approving tenofovir-emtricitabine for use as oral PrEP. The Antiviral Drugs Advisory Committee of the FDA considered the need for postmarketing studies to identify behavioral changes associated with PrEP use (FDA Center for Drug Evaluation and Research, 2012), and the Risk Evaluation and Mitigation Strategy for Truvada® requires the manufacturer to inform prescribers and users that “TRUVADA . . . must be considered as only part of a comprehensive prevention strategy to reduce the risk of HIV-1 infection and that other preventive measures should also be used” (FDA, 2012; Gilead Sciences Inc., 2012, p. 1). Questions about risk compensation behavior have arisen for each of the emerging HIV prevention technologies (Crosby et al., 2012; Eaton & Kalichman, 2007), and they will persist as the field progresses to study new drug candidates, delivery strategies, and mechanisms for preventing infection.

Also known as behavioral disinhibition (Hogben & Liddon, 2008; Paltiel et al., 2009), offsetting behavior (Peltzman, 1975), or moral hazard (Malani, 2008), the dynamic of risk compensation behavior is not unique to the biomedical HIV prevention context. Studies of this phenomenon have focused on behavioral reactions to such disparate interventions as auto safety equipment (Mackay, 1985; McCarthy, 1989; S. Peterson et al., 1995; Streff & Geller, 1988), bicycle helmets (Adams & Hillman, 2001), children’s safety gear (Morrongiello et al., 2007a; Morrongiello et al., 2007b), diet soda (Fowler et al., 2008), low-tar cigarettes (Institute of Medicine, 2001), Lyme disease vaccination (Brewer et al., 2007), and mandated insurance coverage for diabetes (Klick & Stratmann, 2007) or substance use (Klick & Stratmann, 2006), to name a few studies. Among HIV prevention scientists, risk compensation—also called condom migration (Crosby et al., 2012)—has provoked some to advise caution in the dissemination of new prevention strategies, while others dismiss the

idea as improbable or scientifically unfounded (Grady, 2012; R. Grant & McConnell, 2008). Despite these debates, however, the behavioral analyses accompanying trials of biomedical prevention interventions can say little to confirm or dispel risk compensation concerns.

An important reason for this information deficit is the lack of accepted study designs for the identification of risk compensation behavior. To date, there has not been a focused inquiry into the study designs available for assessing this phenomenon. The goals of this Commentary are to describe the mechanism of risk compensation behavior, to identify shortcomings of current study designs for evaluating the existence and extent of this behavior, and to explore alternative study designs for accessing risk compensation effects. IRB approval was not needed for this Commentary because it does not meet the definition of research involving human subjects.

Characterizing the Phenomenon

Descriptions of risk compensation behavior originate in the theory of “risk homeostasis” (Adams, 1995; Hedlund, 2000; Wilde, 2001) which proposes that for every activity, “people accept a certain level of subjectively estimated risk to their health . . . in exchange for the benefits they hope to receive from that activity” (Wilde, 2001, p. 5). To the extent that we control our behaviors, this theory suggests that each of us continually adjusts our risk-taking so that our perceived risk approaches a “target risk level”: the level at which we see the most acceptable trade-off between risks and benefits. This level need not be static, and it may change due to factors such as time or social influences. But at any given point, our target risk level represents what we perceive to be the optimal balance between risk-taking (e.g., sex without condoms) and the potential benefits of risky behavior (e.g., intimacy, sexual pleasure).

When we perceive that our risks or potential benefits have changed, risk homeostasis theory suggests that we respond by altering our behavior in a direction that brings the perceived balance closer to our target risk level (Wilde, 2001). This adjustment is “risk compensation,” and although most discussions of this behavior are concerned with *increases* in risk-taking, this phenomenon also encompasses *decreases* in risk-taking when we perceive that our risks are unacceptably high. For example, knowing that one’s partner is HIV-positive may make someone more likely to use a condom or to avoid unprotected receptive sex (Carballo-Dieuez et al., 2012). Usually, however, discussions of risk compensation behavior focus on ways in which increased behavioral risk-taking may undermine the effectiveness of new health and safety interventions.

Risk homeostasis theory and its corollary mechanism of risk compensation have been criticized, often on the basis that people are not sufficiently rational to calculate their risks or calibrate their behaviors in response to a preventive intervention (McKenna, 1985; O’Neill & Williams, 1998). The mechanism of risk compensation, however, accommodates irrationality at every stage. Individuals’ perceptions of risks and benefits need not be accurate for them to know that they are balancing risks and benefits, or to adjust their behavior *to some extent* when they perceive (however accurately) that the balance has shifted. The theory further does not demand that an individual’s actual risk level remain

constant over time; rather, it stipulates only that changes in risk perceptions will predictably prompt behavioral adjustments in the direction of one's preferred balance of risks and benefits. These adjustments may be modest, or they may be entirely absent if individuals do not have the opportunity or motivation to behave more riskily (e.g., decreased condom use is irrelevant for individuals with no sexual partners, or for individuals who never used a condom in the first place). But even minimal behavioral changes may influence the effectiveness and cost-effectiveness of new HIV prevention technologies. For example, one mathematical model of PrEP's cost-effectiveness among US men who have sex with men (MSM) suggested that a 4.1% increase in the annual number of new sexual partners could fully offset the population-level benefit of a PrEP drug with 50% efficacy, assuming that PrEP is used by 25% of the population with 50% adherence (Desai et al., 2008).

In a summary of risk compensation research, Hedlund has identified four preconditions for an individual risk compensation response: 1) the intervention must be visible to the individual, 2) the intervention must have an effect on the individual that gives rise to the perception of protection, 3) the individual must have a motivation to increase his risk-taking, and 4) the individual must have control and opportunity to adjust his behavior (Hedlund, 2000). These preconditions are fulfilled for HIV prevention technologies such as PrEP, microbicides, and vaccines. For instance, individuals who take oral PrEP will be aware of their product use, and they will expect the pills to reduce their HIV risk. They may desire to have more partners or to use condoms less frequently (but previously did not due to HIV concerns), and they may have opportunities to take these actions while using PrEP. Surveys and qualitative data suggest that some MSM may indeed take more behavioral risks while using PrEP (Brooks et al., 2012; Golub et al., 2010; Krakower et al., 2012; Tripathi et al., 2012; Underhill et al., 2012), although analyses of actual user behavior are still unavailable.

To facilitate the study of risk compensation behavior, it is helpful to consider it as the effect of a psychological stimulus. That is, an individual's increase in risk-taking behaviors is a response to the belief that he or she is protected (to any extent) from harm. In biomedical HIV prevention, this perception has two components: the individual must believe that he is receiving a preventive intervention, and he must believe that the intervention works to reduce his HIV risk. For the ensuing discussion, this two-part perception of protection is the independent variable, and any risk compensation response flows from this belief.

Methodological Limitations of Phase II and Phase III Designs

The study designs currently required for FDA approval of a new drug or device are poorly suited for the assessment of risk compensation behavior. In Phase II and III trials, participants are randomly assigned to receive either a new intervention or a control intervention such as a placebo (Phase II or III) or "usual care" (Phase III). Participants who join a trial may have a range of beliefs about whether the experimental treatment will work; some may be confident that the treatment is efficacious, while others may be unsure or skeptical. Through random assignment, these participants are evenly allocated to different trial arms, and each arm contains participants with a range of beliefs about group assignment and intervention efficacy. Although random assignment will determine the interventions participants *actually receive*, these trials are not designed to produce any systematic

differences between trial arms in what participants *believe*. For this reason, between-arm comparisons in these trials are thoroughly deficient for assessing the link between participants' perceptions of protection and their HIV risk behavior.

Indeed, if participants believed all the messages provided by trial staff, active and control participants in a Phase II/III placebo-controlled trial would have exactly the same perception of protection. In placebo-controlled Phase II/III trials, all participants receive the message, "This pill *may* be the active drug, and if so, the pill *may* work to prevent HIV." Investigators must convey these facts accurately to fulfill the Belmont Report's bedrock principle of respect for participants' autonomy (National Commission, 1979); participants need this information to make considered judgments about trial participation and HIV risk. Consistent messaging across arms also minimizes the potentially confounding influence of placebo effects. But because the active and placebo arms receive the same message, there is no reason to expect that participants' perception of protection—and, therefore, their risk compensation responses—will differ systematically across arms. Instead of evaluating risk compensation behavior, the value of between-arm behavioral comparisons in a placebo-controlled trial is to identify whether the active treatment causes behavioral changes through *biochemical* effects or another mechanism besides changed risk perceptions.

Participants in efficacy and effectiveness studies sometimes know their treatment assignment. For example, participants in male circumcision trials or trials with usual-care controls may know their condition. But all participants in such trials are nonetheless told, "The experimental treatment *may* work to prevent HIV." Given these uncertain messages, participants in the experimental arm may still lack the perception of reduced HIV risk; at the very least, we cannot be certain that they have a higher perception of protection compared to controls. This flaw again undermines the use of between-arm behavioral comparisons to assess risk compensation.

In addition to these deficits, all studies conducted before the approval of a new intervention—including, by definition, all Phase II/III trials—lack external validity in the approximation of risk compensation behavior. Real-world users will receive the interventions *after* they are proven effective, and they will adopt the interventions precisely because they already believe that the technologies work. Because investigators are ethically bound to tell trial participants that treatment efficacy is uncertain, or that group assignment and treatment efficacy are both uncertain, messaging during clinical trials is designed to forestall the perceptions of protection that are essential for risk compensation behavior to take place. To illustrate this point, one participant in the CDC 4323 PrEP safety trial later commented that because he knew he could have received a placebo, it was "[his] responsibility to continue living HIV-free" during the trial (Center for HIV Identification, 2009, p. 10; Leibowitz et al., 2011). Even if he had known his group assignment, he may still have been concerned that the experimental drug was ineffective. Thus, even Phase III trials in which participants are aware of their treatment condition are not structured to provide a valid test of risk compensation behavior.

Some investigators have analyzed behavioral data from Phase II or III trials longitudinally, assessing the behaviors of *all* participants from baseline through later stages of the trial. This

strategy has been used in several PrEP trials, which found that overall risk behavior declined during the study (Baeten et al., 2012; R. M. Grant et al., 2010; L. Peterson et al., 2007). These analyses are sometimes cited as evidence that risk compensation behavior is unlikely or did not occur among PrEP users (Jay & Gostin, 2012; National Alliance, 2012), and some have suggested that if risk compensation behavior is not observed in clinical trials, it is proof that the theory has failed (R. Grant & McConnell, 2008). Other commentators have questioned these conclusions, in part because trial participants receive intensive behavioral counseling (Mascolini, 2012), and in part because the repeated assessment of sexual behavior during a trial may itself influence participants' actions. But these are not the only defects that make longitudinal comparisons an inapposite test of risk compensation. These one-group designs are unhelpful precisely because they fail to isolate the independent variable of interest: the user's belief that he or she is protected from HIV. Longitudinal analyses of trial participants do not demonstrate the relationship between participants' perceptions of group assignment, perceptions of intervention efficacy, and risk-taking behaviors. Moreover, it may be misleading to cite these analyses to support the proposition that risk compensation behavior is absent or unlikely. In order to assess risk compensation behavior accurately, a different study design is needed.

An Ideal Methodology with Fatal Ethical Flaws

The gold standard for identifying the effect of a specific stimulus is the randomized controlled trial, in which participants are randomly assigned to receive the stimulus or to serve as controls (Schulz et al., 2010). Barring a failure of randomization (which becomes less likely as sample size increases), randomly assigning participants to study arms evenly distributes known and unknown confounders across all arms. Any measurable difference between the two groups at follow-up, therefore, may be attributed to the intervention rather than to a confounder.

As discussed above, investigators routinely use randomized designs to assess the efficacy of new HIV prevention technologies. But no randomized trial has yet examined the effect of the *perception* that one has received an efficacious HIV prevention technology. The methodologically ideal study design for assessing risk compensation behavior would use this approach, randomly assigning participants to an active arm that induces them to believe that they have received an efficacious HIV prevention technology ("This intervention will reduce your risk of HIV infection"), or to a control arm that induces the perception of unchanged risk ("Your risk of HIV infection will not change"). The study arms would ideally be equivalent in all other respects; for instance, if the investigators provide an HIV prevention technology, they would provide it to both groups. Under this design, any behavioral differences observed between the active and control arms at follow-up would be attributable to the *messages* that participants receive, not to the intervention itself. It would be important to measure participants' actual perceptions of protection as a mediator in this analysis, as some participants may not wholly believe the study's statements about efficacy. To further maximize external validity in this type of trial, experimental-arm participants should receive the same efficacy messages that real-world users would receive. For this reason, an externally valid study of risk compensation could only be done during Phase IV testing, after

efficacy and effectiveness are known. A study design with all of these features would come closest to assessing the behavioral effects of perceived protection from HIV infection.

Using this model, a methodologically rigorous trial of PrEP-associated risk compensation could provide all participants with PrEP pills, but participants would be randomized into two groups receiving different messages. The experimental study arm would receive an accurate estimate of the pills' efficacy for preventing infection, based on prior testing in Phase II and III trials. The control study arm, meanwhile, would deceptively be told that the pills are ineffective placebos. Or alternately, and more ethically suspect, all participants could receive placebos, but the active study arm would deceptively be told that the pills reduce HIV risk.

Important ethical defects should prevent both variations of this study from taking place, regardless of the potential to isolate risk compensation effects. This design violates multiple Belmont Report principles, including the need for maximizing benefits (beneficence) and minimizing harms (non-maleficence) (National Commission, 1979). The foremost flaw is a lack of equipoise: the need for genuine uncertainty about the relative merits of two conditions in a randomized trial (Miller & Joffe, 2011). The HIV prevention literature provides an empirical basis to suspect that participants who believe they are protected will take more behavioral risks; although there may be genuine uncertainty about the *magnitude* of this effect, there is little uncertainty about its *direction*. Consider the variation where both arms receive efficacious PrEP, but only the active arm receives accurate messaging. Active-group participants who increase their risk-taking may have a net lower HIV risk compared to baseline, so long as their additional risk-taking does not fully offset PrEP's benefit. But their increased behavioral risks would disadvantage them compared to the control group, and their risks for other STIs may rise compared to baseline. Simultaneously, control-group participants who believe that the pills are ineffective may decline to take them, thereby failing to maximize PrEP's benefits and incurring an elevated risk of HIV infection compared to the active arm. Neither arm would obtain the maximum benefits of the study (failing beneficence), and both groups may sustain harm (failing non-maleficence). In the variation where both arms receive a placebo, but the active arm is deceived into believing it is efficacious PrEP, risk compensation would predictably expose the active arm to a *greater* risk for HIV infection compared to baseline. This design is fatally flawed.

The second fundamental ethical objection to this study is the need for deception, and the corresponding violation of the Belmont Report principle of respect for autonomy (National Commission, 1979). This study design depends on inducing the perceptions of protection in only the active arm, so accurately informing all participants of the design would undermine validity. But withholding accurate information undermines participants' opportunity to exercise judgment about participation and ongoing risk behavior. This deception can have meaningful adverse effects in both study variations, including increased risk for HIV and other STIs. Although the Belmont principles may tolerate deception for studies meeting certain requirements, including that there are "no undisclosed risks . . . that are more than minimal," an increased likelihood of HIV infection exceeds minimal risk.

The Phase IV No-Treatment Controlled Trial

The problem of deception, but not equipoise, can be cured by changing the ideal study design to a second-best alternative. As designed, standard placebo-controlled Phase II and III trials can show that HIV prevention technologies do not induce behavioral changes through biochemical or physiological mechanisms (Underhill, 2011). This evidence sets the stage for a no-treatment controlled trial during Phase IV, in which participants are randomized to receive either the effective intervention, or no treatment (e.g., a waitlist control). In this trial, two conditions vary across trial arms – 1) the receipt of an intervention, and 2) the message that one has received an effective intervention for preventing HIV. If behavioral differences are observed across the trial arms, they could be due to either of these conditions. But if earlier effectiveness trials have shown that the intervention itself does not induce behavioral change, then behavioral differences between the two groups could definitively be attributed to the differences in their perceptions of benefit.

This second-best alternative would be a methodologically rigorous test of risk compensation behavior. But although deception is not necessary for the study, the ethical problem of equipoise remains. Unless there is a genuine possibility that risk compensation will be sufficient to negate or reverse the benefit of the intervention, it is likely that the experimental group receiving the efficacious intervention will be better off than the controls. Ethical guidance for the use of placebos or no-treatment controls varies, but many guidance documents would counsel against this design due to the Belmont principles of beneficence and non-maleficence. Under CIOMS guidance, for example, placebos or no-treatment controls may only be used “when there is no established effective intervention,” if withholding an effective intervention “would expose participants to at most temporary discomfort,” or if the use of a placebo is scientifically necessary and will not “add any risk of serious or irreversible harm” (Council, 2002). The Declaration of Helsinki prescribes similar standards (World Medical Association, 2008). If intervention efficacy has already been established in Phase II/III, a no-treatment controlled trial may not meet these standards.

The Two-Trial or Nested Trial Strategy

A new solution to the dilemmas posed by single-trial methods is to employ a study design recently proposed by Malani to detect placebo effects, which may be used during Phase II/III testing (Malani, 2006, 2008). Malani’s strategy relies on obtaining data from two effectiveness trials with varying probabilities of assignment to the active arm. For example, suppose that Trial 1 participants are allocated to active and placebo arms in a 1:1 ratio. But Trial 2 participants are allocated to active and placebo arms with a higher probability of assignment to the active arm, such as a 2:1 ratio. Participants in Trial 2 will know that they are more likely to be in the active arm, and therefore should have higher expectations of receiving the experimental drug. If participants expect that the experimental drug will be efficacious, their expectations of benefit should be higher in Trial 2. To identify the marginal impact of these expectations on behavior, investigators can then compare the behaviors of participants in the active arm of Trial 2 against the participants in the active arm of Trial 1. If the trial populations are similar in all other respects, behavioral differences between the two active arms could be attributed to differences in the expectation of benefit.

One strength of this approach is its efficiency; it takes advantage of study designs already required for regulatory approval, and it would require only a minor alteration in protocols normally used to determine efficacy and effectiveness. This two-trial strategy, however, has weaknesses as applied to the investigation of risk compensation behavior. First, it does not remedy the problem posed by participants' uncertainty regarding whether the experimental drug is indeed beneficial. Participants will still receive the message, "the active drug *may* work," which does not allow the study to replicate the perceptions of benefit that will drive risk compensation behavior among real-world users. This problem could be solved in part by asking participants to identify their perceptions of product efficacy, and then conducting analyses only among participants who report believing that the experimental intervention is effective. Second, the validity of this design will depend on participants' understanding of probability, which requires further testing. Third, if the trials are conducted sequentially, participants in Trial 2 may adjust their behaviors after learning the results of Trial 1. Fourth, participants in two separate trials may differ for many other reasons, including time or geographical location. The third and fourth weaknesses could be remedied by using a nested trial design instead of two sequential trials. That is, one large group of participants could first be randomized to either participate in Trial 1 or Trial 2, then separately randomized to their treatment group. This would evenly distribute confounders across the two separate trials, making comparisons between the two active arms (or control arms) more rigorous.

With the modifications suggested here, the two-trial or nested trial strategy solves both the ethical dilemmas of equipoise and deception. Participants would receive accurate information about their probability of assignment to trial arms, and investigators would be genuinely uncertain about the relative merits of the different conditions. This design would improve upon the current behavioral analyses in efficacy and effectiveness trials, and biomedical HIV prevention investigators should consider using this approach. But this design remains an imperfect test of risk compensation behavior due to external validity problems; trial participants may still lack the perceptions of real-world, post-approval users.

Methodological Additions to Phase II and Phase III Trials

Each of the rigorous study designs described thus far has attempted to manipulate the independent variable of interest: the perception of reduced HIV risk due to an effective intervention. But if this is impossible, an alternative is to identify participants who already have the perceptions of interest, and then to assess their behavior. This Commentary encourages investigators in Phase II and Phase III trials to include supplementary measures to identify participants who believe they are receiving an efficacious intervention. These measures should assess participants' perceived group assignment, perceived efficacy of the experimental intervention, and perceived efficacy of the placebo. Moreover, to account for the possibility that some participants have an incomplete understanding of the study design, investigators should also ask directly about perceived efficacy without mentioning group assignment (e.g., "Do you believe your pills work to prevent HIV?"). Investigators can then compare the behaviors of participants who believe they are receiving an efficacious intervention against participants who lack these beliefs.

Table 1 identifies 27 potential subgroups of participants in a Phase II/III trial, depending on perceived group assignment (experimental, uncertain, or control), perceived efficacy of the experimental intervention (efficacious, uncertain, or inefficacious), and perceived efficacy of the placebo (efficacious, uncertain, or inefficacious). In 7 subgroups, participants believe that they have received an efficacious intervention. In another 7 subgroups, participants believe that they have received an inefficacious intervention. And in the remaining 13 subgroups, participants are genuinely uncertain whether the pill they are taking prevents HIV. Comparisons among these 3 categories can provide an initial indication of risk compensation behavior, depending on participants' perception of whether they have received an efficacious product.

To classify participants correctly, investigators should regularly ask each participant to identify his perceived trial arm. The investigators of the iPrEx trial (testing daily oral PrEP) asked participants to identify their perceived group of assignment during week 12 (R. M. Grant et al., 2010). Participants responded to a 5-item scale ranging from "Strongly [experimental drug]" to "Strongly placebo," with options for "Don't know" and "Decline to state." Of all participants, 23% believed that they were receiving the experimental drug, while 10% believed that they were receiving placebo. The investigators concluded that the even distribution of responses among actual experimental and control participants indicated a high quality of blinding, but missed an opportunity to link these perceptions to participant behavior (Underhill, 2011).

Knowing participants' perceived group assignment is helpful, but incompletely useful for identifying participants with a perception of reduced HIV risk. In order to use these data effectively, it is also necessary to ask participants to identify perceived product efficacy: the extent to which they believe that their intervention is efficacious for preventing HIV. Of the 23% of iPrEx participants who believed they took PrEP, some may have believed the drug to be efficacious, while others may have believed otherwise. Those with little faith in the drug would lack the perceptions of benefit necessary for risk compensation, but those who believed in the drug's efficacy would have the requisite beliefs. Behavioral analyses could then compare participants who believed they received an efficacious drug, those who believed they received an inefficacious placebo, and those who were unsure of group assignment or product efficacy. Further analyses could also incorporate participants who believed they were receiving the placebo, but who also believed that the placebo could prevent HIV; although these beliefs would run counter to the messages provided by investigators, these perceptions may reflect a "preventive misconception" (Microbicide Trials Network, 2012). Here again, in case participants do not understand the study design completely, investigators can account for this confusion by adding a more direct question about perceived product efficacy (e.g., "Do you think your [intervention] works to prevent HIV?").

Investigators could use similar strategies to identify risk compensation in unblinded trials, such as any further tests of male circumcision. Supplementary questionnaires could identify circumcised participants who believe that circumcision has reduced their HIV risk, comparing them to control-group participants and to circumcised participants lacking perceptions of protection.

To maximize the value of these supplementary analyses, it would also be useful to conduct qualitative interviews among randomly selected participants in each category of interest. Qualitative methodologies are ideally suited for exploring the complex mechanisms of risk perception and behavioral adjustment. Interview agendas investigating these themes could probe perceptions of product efficacy, reasons for perceived product efficacy and/or perceived group assignment, and connections between perceived product efficacy and behavioral decision-making. A mixed-methods study integrating between-group comparisons and qualitative interviews would be well-suited for identifying preliminary indications of risk compensation behavior, as well as illuminating potential opportunities for behavioral counseling and user education. To minimize the potential for response bias or social desirability bias, it may help to require that interviews be conducted by someone other than the trial's clinical staff.

The analyses proposed here have limitations. Nonrandomized designs are vulnerable to confounders, and one important confounder in this analysis may be optimism bias (Helweg-Larsen & Shepperd, 2001). Participants prone to optimism bias may be more likely to believe that they are in the active treatment arm, and also more likely to believe that the active treatment is efficacious. If optimism bias also influences or co-varies with risk behaviors, it would be an important confounder in the correlation between perceived product efficacy and risk behavior. Side effects are another potential confounder; participants who experience side effects may be more likely to believe that they are in the experimental arm, but some side effects may simultaneously influence libido or sexual activity. A third potential confounder may be adherence. Participants who suspect that they are taking placebos may have poorer adherence to the drug regimen than participants who believe they are in the active group. But adherence may also influence risk compensation behavior; for example, high adherence may reinforce perceptions of drug effectiveness. When it is possible to measure and account for known confounders, such as optimism bias, side effects, and adherence, this should be done. Analyses should also account for baseline sexual behavior among each group.

Another limitation of this approach is the potential instability of participants' perceptions. Perceptions of group assignment and intervention benefit may change over time, making it difficult to pinpoint whether participants' behaviors actually took place while they held the perceptions of interest. Self-reported perceptions will also be vulnerable to reporting bias, as participants may not wish to disclose beliefs that contradict investigators' messages about the uncertainty of group assignment and intervention benefit. Finally, problems of external validity are inevitable in preapproval testing, as real-world users will receive different product messaging about efficacy.

Despite these limitations, however, appending the proposed questions and analyses to Phase II and III trials would be an inexpensive way to obtain a preliminary indication of risk compensation behavior before new interventions are approved for use. In fact, a supplementary protocol for the VOICE microbicides study is already collecting data on "preventive misconception," identifying whether participants in the trial believe that they are receiving an efficacious prevention intervention (Microbicide Trials Network, 2012). A measure of preventive misconception would enable the type of analyses envisioned by this

Commentary. This is not to say that new HIV prevention technologies should be withheld or denied FDA approval if risk compensation behavior occurs; this is a separate question that requires analysis from multiple perspectives, including public health, ethics, human rights, and the law (Underhill, 2013). From a public health perspective, however, understanding preliminary indications of risk compensation behavior can inform the development of behavioral interventions to support and educate the users of new technologies, with the goal of maximizing product effectiveness. These proposed additions to Phase II and Phase III trials would not require changes to the processes already required for regulatory approval, but they would provide a more rigorous test of risk compensation behavior than the longitudinal and between-group comparisons that currently accompany effectiveness trials.

Postmarketing Studies and Other Designs

After an intervention has been tested in Phase I through Phase III trials and approved for use, investigators have opportunities to assess behavioral adjustments among actual users. This Commentary has already discussed several methodologically rigorous ways to identify risk compensation behavior among this group (a deception trial or a trial with no-treatment controls), but ethical objections will generally prevent these studies from taking place.

The ideal replacement for a randomized manipulation of participant perceptions would be to take advantage of a distribution venue in which potential users already obtain the intervention – in this case, a new HIV-prevention technology – through a lottery system. For example, a clinic with funding to support only a limited number of PrEP users may randomly select new patients from a waiting list. This is by necessity a no-treatment controlled trial. “Winning” and “losing” effects may be potential confounders in analyses comparing lottery winners to those who are waitlisted or denied an intervention they believe to be effective; for example, someone who wanted but was actively denied PrEP may behave differently from someone who has not had this experience. Studying a naturally occurring lottery may also raise questions about the ethics of necessarily using resource-limited settings for this type of research. This study design, however, would come closest to a rigorous test of how the perception of reduced HIV risk impacts behavior.

Barring a natural lottery, postmarketing studies of risk compensation behavior may use several alternative designs. These include cohort studies comparing product users to nonusers or the general population over time (like many open-label extension studies), population-level longitudinal studies comparing behavior before and after the new technology is introduced, correlational studies seeking relationships between product uptake and behavior over time or across geographical areas, or simulation studies (Glendon, 1996) in which participants respond to hypothetical scenarios about their likely behavior in situations with or without the new technology. With the exception of simulations, these designs have the advantage of taking place among real-world users in the context of real-world product messaging. These studies will provide externally valid tests of risk compensation responses to a new technology, and these data are essential for developing behavioral interventions that support product users. Postmarketing investigators should also seize opportunities for longitudinal analyses to gauge whether changes in risk behavior are temporary or sustained; for example, a risk compensation response may be pronounced

immediately after a new technology is introduced, but this effect may attenuate over time as the new technology becomes less salient. Or conversely, some qualitative data suggests that risk compensation may also occur with a delay after product adoption, once the user is confident that the product is effective (Brooks et al., 2012).

Despite these advantages, all nonrandomized postmarketing studies present a trade-off between external validity and methodological rigor. When the option to actively manipulate user perceptions is methodologically or ethically unavailable, all study designs become vulnerable to known and unknown confounders. Changes in risk behavior over time, for example, could arise from shifting cultural norms entirely separate from changes in perceptions of risk, such as changes in drug or alcohol use or new venues for meeting sexual partners. Even if population-level changes in risk behavior are associated with the use of prevention technologies, it will be unclear whether the perception of reduced HIV risk is indeed the mechanism driving this behavior.

Conclusions

This Commentary has evaluated a variety of study designs for the identification of risk compensation behavior. Due to inherent methodological limitations, the current behavioral data arising from Phase II and Phase III trials are insufficient to approximate risk compensation responses among real-world users of new HIV prevention technologies. The ideal study designs for the assessment of risk compensation are unavailable due to ethical flaws, such as the lack of equipoise or the need for deception. But several study designs present opportunities to better approximate risk compensation responses during Phase II, III, and IV testing.

Based on this review and Commentary, the most methodologically rigorous, externally valid, and ethically acceptable design for assessing risk compensation behavior is to take advantage of a naturally occurring experiment during roll-out and Phase IV testing. After product approval, postmarketing studies should identify behavioral responses among actual product users. A naturally occurring experiment (e.g., a clinic with limited resources distributes PrEP by lottery) could stand in for the rigorous but ethically suspect study manipulating users' perceptions. If this opportunity does not naturally arise, postmarketing studies should continue using nonrandomized or simulation methods to link product use, perceptions of reduced HIV risk, and user behaviors. These designs presently account for most assessments of risk compensation behavior among product users, and although they lack the methodological rigor of a randomized approach, external validity is a key strength.

Before products are approved, this Commentary has identified several ways for Phase II and III trials to better approximate risk compensation behavior with a minimal loss of efficiency in several ways. First, this Commentary would recommend the use of a two-trial or nested trial approach, although it will be important to further evaluate the study design based on participants' understanding of probability. Second, this Commentary recommends that Phase II/III trials include supplementary questions, qualitative interviews, and analyses regarding participants' perceptions of group assignment and product efficacy. These two approaches (a nested design with supplementary analyses) could also be used together. Although neither

approach would provide an externally valid test of risk compensation responses, both would improve on the existing behavioral data arising from Phase II and Phase III testing. The results of such analyses would be highly useful for developing behavioral counseling and messaging to accompany the initial dissemination of a new prevention option.

This Commentary has not addressed the question of what should be done with data on risk compensation behavior once they have been obtained. Given prevailing concern about risk compensation effects, identifying behavioral adjustments during the Phase II and Phase III stages of product testing may bolster opposition to the approval and dissemination of these products for general use. Data on risk compensation responses among actual users during Phase IV or postmarketing testing may also be used to oppose widespread product use or financing. This is not the goal of this Commentary nor should it be the goal of a rigorous assessment of risk compensation behavior. Instead, these study designs can yield essential information for the development of behavioral interventions to support potential users in making decisions about adopting new products, and to support actual users during the period of product use. In order to design delivery packages for new HIV prevention products that optimize user behaviors, it is essential to conduct research specifically tailored to the internally and externally valid assessment of these behaviors. Moreover, if methodologically rigorous studies show that risk compensation is minimal or absent, they would provide a useful empirical basis to dispel unfounded concerns about user responses to product rollout.

If risk compensation behavior is detected, it may be necessary to reevaluate attitudes towards such behavior in order to respond productively. Increases in risk-taking can reduce the effectiveness and cost-effectiveness of HIV prevention technologies, potentially even reversing their preventive benefits if risk compensation is extreme or efficacy is low. Increased risk-taking may also facilitate the spread of other STIs. But it is also important to recognize the positive benefits that product users and their partners may gain from adjusting their behaviors. Product users may perceive that increases in risk-taking, such as discontinuing condoms, will strengthen their relationships, improve their sexual satisfaction, or increase their intimacy with partners. In this view, sexual risk compensation behavior could be reframed as a means of exchanging one benefit (reduced HIV risk) for another benefit that the user values (e.g., intimacy; pleasure; increased income for sex workers who receive extra compensation for sex without condoms (Gertler et al., 2005)). For some product users, a mixed allocation of benefit may seem most desirable – they may want to reduce their HIV risk, but they may also be comfortable giving up some of that protection, such as by having sex without condoms. From the public health and healthcare payer perspective, it is most desirable for all product users to avoid increases in behavioral risk-taking, thereby maximizing product effectiveness and avoiding the escalation of other STIs. But we cannot respond realistically to risk compensation behavior without appreciating users' motivations and perceptions of benefit. Risk compensation behavior does not necessarily mean the failure of a new HIV prevention technology; when other values are considered, some risk compensation behavior may be rational and potentially even value-maximizing for some product users. The field remains responsible, however, for identifying ways to make these individual decisions as well-informed as possible.

Currently, the lack of behavioral data on risk compensation allows for continuing speculation about users' behavioral responses to new prevention technologies. In some cases, such as recent controversies over the dissemination of the HPV vaccine (Kahan, 2010) or the approval of Truvada® as PrEP (Grady, 2012) these concerns have fueled efforts to oppose access to efficacious technologies. It is now essential to conduct research that answers these questions directly. A nuanced and empirically derived understanding of risk compensation behavior will fill an important gap in the HIV prevention field, and investigators should consider a range of study designs to meet this need.

Acknowledgments

The author is funded by NIH grant 1-K01-MH093273 (PI: Underhill), and I am grateful for Kenneth H. Mayer's primary mentorship. I am also grateful to the Yale Center for Interdisciplinary Research on AIDS, the Brown/Tufts/Lifespan Center for AIDS Research, and Yale Law School for support. Anonymous peer reviewers provided helpful suggestions for revision.

References

- Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV in women. *Science*. 2010 Jul 19;10.1126/science.1193748
- Adams, J. Risk. University College of London Press; 1995.
- Adams J, Hillman M. The risk compensation theory and bicycle helmets. *Injury Prevention*. 2001; 7:343. [PubMed: 11770666]
- Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *New England Journal of Medicine*. 2012; 367:399–410. [PubMed: 22784037]
- Brewer NT, Cuite CL, Herrington JE, Weinstein ND. Risk compensation and vaccination: Can getting vaccinated cause people to engage in risky behaviors? *Annals of Behavioral Medicine*. 2007; 34:95–99. [PubMed: 17688401]
- Brooks RA, Landovitz RJ, Kaplan RL, Lieber E, Lee SJ, Barkley TW. Sexual risk behaviors and acceptability of HIV pre-exposure prophylaxis among HIV-negative gay and bisexual men in serodiscordant relationships: a mixed methods study. *AIDS Patient Care and STDs*. 2012; 26:87–94. [PubMed: 22149764]
- Carballo-Diequez, A.; Balan, I.; Frasca, T.; Dolezal, C.; Valladares, J. Use of a rapid HIV home test to screen potential sexual partners prevents HIV exposure in a high-risk sample of MSM. XIX International AIDS Conference (p. TUPDC0304); Washington, D.C., USA. 2012.
- Center for HIV Identification, P., and Treatment Services. Preparing for PrEP: A stakeholder's dialogue. Atlanta, GA: 2009. p. 18
- Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *New England Journal of Medicine*. 2011; 365:493–505. [PubMed: 21767103]
- Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for biomedical research involving human subjects. Geneva, Switzerland: CIOMS; 2002.
- Crosby RA, Ricks J, Young A. Condom migration resulting from circumcision, microbicides and vaccines: brief review and methodological considerations. *Sexual Health*. 2012; 9:96–102. [PubMed: 22348637]
- Desai K, Sansom SL, Ackers ML, Stewart SR, Hall HI, Hu DJ, et al. Modeling the impact of HIV chemoprophylaxis strategies among men who have sex with men in the United States: HIV infections prevented and cost-effectiveness. *AIDS*. 2008; 22:1829–1839. [PubMed: 18753932]
- Eaton LA, Kalichman SC. Risk compensation in HIV prevention: Implications for vaccines, microbicides, and other biomedical HIV prevention technologies. *Current HIV/AIDS Reports*. 2007; 4:165–172. [PubMed: 18366947]

- FDA. Truvada for PrEP fact sheet: Ensuring safe and proper use. US Department of Health & Human Services; 2012.
- FDA Center for Drug Evaluation and Research. Antiviral Drugs Advisory Committee Meeting: Draft Questions to the Committee. 2012
- Fowler SP, Williams K, Resendez RG, Hunt KJ, Hazuda HP, Stern MP. Fueling the obesity epidemic? Artificially sweetened beverage use and long-term weight gain. *Obesity*. 2008; 16:1894. [PubMed: 18535548]
- Gertler P, Shah M, Bertozzi SM. Risky business: The market for unprotected commercial sex. *Journal of Political Economy*. 2005; 113:518–550.
- Gilead Sciences Inc. Truvada: Risk Evaluation and Mitigation Strategy. 2012
- Glendon AI. A review of risk homeostasis theory in simulated environments. *Safety Science*. 1996; 22:15.
- Golub SA, Kowalczyk W, Weinberger CL, Parsons JT. Preexposure prophylaxis and predicted condom use among high-risk men who have sex with men. *Journal of Acquired Immune Deficiency Syndromes*. 2010; 54:548–555. [PubMed: 20512046]
- Grady, D. FDA advisory panel backs preventive use of HIV drug. *The New York Times*; New York, NY: 2012. p. A1
- Grant, R.; McConnell, J. The trouble with risk compensation. XVII International AIDS Conference; Mexico City, Mexico. 2008. p. CDC0253
- Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New England Journal of Medicine*. 2010
- Hedlund J. Risky business: safety regulations, risk compensation, and individual behavior. *Injury Prevention*. 2000; 6:82–90. [PubMed: 10875661]
- Helweg-Larsen M, Shepperd JA. Do Moderators of the Optimistic Bias Affect Personal or Target Risk Estimates? A Review of the Literature. *Personality and Social Psychology Review*. 2001; 5:74–95.
- Hogben M, Liddon N. Disinhibition and risk compensation: scope, definitions, and perspective. *Sexually Transmitted Diseases*. 2008; 35:1009–1010. [PubMed: 18936724]
- Institute of Medicine. Clearing the smoke: Assessing the science base for tobacco harm reduction. Washington, DC: National Academy of Sciences; 2001.
- Jay JS, Gostin LO. Ethical challenges of preexposure prophylaxis for HIV. *JAMA*. 2012; 308:867–868. [PubMed: 22847147]
- Kahan D. Who fears the HPV vaccine, who doesn't, and why? An experimental study of the mechanisms of cultural cognition. *Law and Human Behavior*. 2010; 34:501. [PubMed: 20076997]
- Klick J, Stratmann T. Subsidizing addiction: Do state health insurance mandates increase alcohol consumption? *Journal of Legal Studies*. 2006; 35:175.
- Klick J, Stratmann T. Diabetes treatments and moral hazard. *Journal of Law and Economics*. 2007; 50:519.
- Krakower, D.; Mimiaga, M.; Rosenberger, J.; Novak, D.; Mitty, J.; White, J., et al. Anticipated risk compensation with pre-exposure prophylaxis use among North American men who have sex with men using an internet social network. XIX International AIDS Conference; Washington, D.C., USA. 2012. p. TUAC0302
- Leibowitz AA, Parker KB, Rotheram-Borus MJ. A US policy perspective on oral preexposure prophylaxis for HIV. *American Journal of Public Health*. 2011; 101:982–985. [PubMed: 21493945]
- Mackay M. Seat belts and risk compensation. *BMJ*. 1985; 291:757–758. [PubMed: 3929928]
- Malani A. Identifying placebo effects with data from clinical trials. *Journal of Political Economy*. 2006; 1:236.
- Malani A. Regulation with placebo effects. *Duke Law Journal*. 2008; 58:411. [PubMed: 19353835]
- Mascolini M. Who's prepared to make PrEP work? *Research Initiative Treatment Action*. 2012; 17:5–27.
- McCarthy M. The benefit of seat belt legislation in the United Kingdom. *Journal of Epidemiology and Community Health*. 1989; 43:218–222. [PubMed: 2607298]

- McKenna FP. Do safety measures really work? An examination of risk homeostasis theory. *Ergonomics*. 1985; 28:489–498.
- Microbicide Trials Network. MPN-003C-01 – Protocol for PREMIS: Preventive misconception in HIV prevention trials. 2012
- Miller FG, Joffe S. Equipoise and the dilemma of randomized clinical trials. *New England Journal of Medicine*. 2011; 364:476–480. [PubMed: 21288100]
- Morrongiello BA, Lasenby J, Walpole B. Risk compensation in children: Why do children show it in reaction to wearing safety gear? *Journal of Applied Developmental Psychology*. 2007a; 28:56–63.
- Morrongiello BA, Walpole B, Lasenby J. Understanding children's injury-risk behavior: Wearing safety gear can lead to increased risk taking. *Accident Analysis and Prevention*. 2007b; 39:618–623. [PubMed: 17112456]
- National Alliance of State & Territorial AIDS Directors. Pre-exposure prophylaxis (PrEP): Health department issues for consideration. NASTAD; 2012.
- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report. U.S. Department of Health & Human Services; 1979.
- O'Neill B, Williams A. Risk homeostasis hypothesis: a rebuttal. *Injury Prevention*. 1998; 4:92–93. [PubMed: 9666359]
- Paltiel AD, Freedberg KA, Scott CA, Schackman BR, Losina E, Wang B, et al. HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. *Clinical Infectious Diseases*. 2009; 48:806–815. [PubMed: 19193111]
- Peltzman S. The effects of automobile safety regulation. *Journal of Political Economy*. 1975; 83:677.
- Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: A phase 2, doubleblind, randomized, placebo-controlled trial. *PLoS Clinical Trials*. 2007; 2:e27. [PubMed: 17525796]
- Peterson S, Hoffer G, Millner E. Are drivers of airbag-equipped cars more aggressive? A test of the offsetting behavior hypothesis. *Journal of Law and Economics*. 1995; 38:251.
- Rekks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *New England Journal of Medicine*. 2009; 361:2209–2220. [PubMed: 19843557]
- Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010; 340:c332. [PubMed: 20332509]
- Streff FM, Geller ES. An experimental test of risk compensation: Between-subject versus within-subject analyses. *Accident Analysis and Prevention*. 1988; 20:277–287. [PubMed: 3415759]
- Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. *New England Journal of Medicine*. 2012; 367:423–434. [PubMed: 22784038]
- Tripathi, A.; Whiteside, YO.; Scanlon, C.; Duffus, WA. Perceptions and attitudes about pre-exposure prophylaxis (PrEP) among seronegative partners and potential of sexual disinhibition associated with the use of PrEP. XIX International AIDS Conference; Washington, D.C., USA. 2012.
- Underhill K. Preexposure chemoprophylaxis for HIV prevention. *New England Journal of Medicine*. 2011; 364:1374. author reply 1374–1375. [PubMed: 21470023]
- Underhill K. Risk-taking and rulemaking: Addressing risk compensation behavior through FDA regulation of prescription drugs. *Yale Journal on Regulation*. 2013 in press.
- Underhill, K.; Morrow, K.; Operario, D.; Ducharme, R.; Kuo, C.; Mayer, K. Project PrEP Talk: An in-depth qualitative analysis of PrEP acceptability, expectations and risk compensation beliefs among United States MSM. XIX International AIDS Conference; Washington, D.C., USA. 2012. p. TUPD0306
- Wilde, GJS. Target Risk 2: A new psychology of safety and health. Toronto, Ontario: PDE Publications; 2001.
- World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. 2008.

Table 1

Beliefs that would support risk compensation behavior among participants in placebo-controlled trials

Perception of experimental drug efficacy	Perception of placebo efficacy	Perception of group assignment		
		Experimental group	Unsure of group assignment	Placebo group
Experimental drug is efficacious	Placebo is efficacious	Risk compensation	Risk compensation	Risk compensation
	Unsure whether placebo is efficacious	Risk compensation	Uncertain	Uncertain
	Placebo is inefficacious	Risk compensation	Uncertain	No risk compensation
Unsure whether experimental drug is efficacious	Placebo is efficacious	Uncertain	Uncertain	Risk compensation
	Unsure whether placebo is efficacious	Uncertain	Uncertain	Uncertain
	Placebo is inefficacious	Uncertain	Uncertain	No risk compensation
Experimental drug is inefficacious	Placebo is efficacious	No risk compensation	Uncertain	Risk compensation
	Unsure whether placebo is efficacious	No risk compensation	Uncertain	Uncertain
	Placebo is inefficacious	No risk compensation	No risk compensation	No risk compensation

Dark shading (Risk compensation) = Participants hold the beliefs presumed necessary for risk compensation to take place. Light shading (No risk compensation) = Participants do not hold the beliefs necessary for risk compensation to take place. No shading (Uncertain) = Participants' beliefs do not predict any specific results according to the risk compensation model.