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# Ethical Concerns About Non-Active Conditions in Smoking Cessation Trials and Methods to Decrease Such Concerns

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## Abstract

Many have questioned whether it is ethical to assign participants in a research trial to a non-active control condition (e.g. a placebo or attention-only control) when a) the disorder under study is serious, b) validated treatment is available, and c) harm may occur if treatment is not given. This ethical concern may apply to studies of controlled trials of treatments for drug dependence. The current paper examines this concern for trials of nicotine dependence because there are multiple validated treatments available. The major harm from assignment to a non-active condition in such a trial could occur if failure to quit discourages smokers from trying to quit again. Whether this harm actually occurs is unclear. Potential harms from non-active conditions may be mitigated by a) provision of more explicit information in the consent process, b) inclusion of only those who have failed optimal treatment, c) provision of validated treatment via a different modality, d) tests of the new treatment as an add-on to standard treatment, e) use of dose-response design, f) use of unequal randomization designs, g) use of stopping rules, h) provision of optimal therapy to those who fail during the study, or i) comparison of the experimental treatment vs. standard treatment. Empirical research to inform ethical analysis of non-active conditions in drug abuse research is suggested.

### Keywords

control groups; ethics; methods; placebo; smoking; smoking cessation; tobacco use cessation

## 1. Introduction

Randomized controlled trials (RCTs) using a non-active control (e.g., a placebo or attention-only condition) are thought to be the best test of the specific efficacy of medical or psychological interventions (Spilker 2000). However, some have argued that it is unethical to assign persons to a non-active control condition when a) a serious disease is being treated, b) proven treatment exists, and c) significant or irreversible harm may occur if treatment is not delivered (Emanuel & Miller 2001; Forster et al. 2001; US Food and Drug Administration. 2001; Huston & Peterson 2001; Weiss Roberts et al. 2001; Rothman 1994; Temple & Ellenberg 2000; Ellenberg & Temple 2000; Tollman 2001; Carpenter et al. 2003). This ethical concern might apply to RTCs of treatments for drug dependence because drug dependence is a serious disorder with validated treatments (Kleber et al. 2006) (www.cochranelibrary.org).

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The current paper reviews whether harm from assignment to a non-active condition might occur in RCTs of treatments for nicotine dependence. The author chose this dependence disorder for three reasons. First, smoking cessation the most important behavioral change an individual can do to improve his/her health (US Department of Health and Human Services 1990), yet quit rates with treatment are still low;(The Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel et al. 2008) thus, continued evaluation of new treatments is essential. Second, seven well-accepted proven pharmacotherapies and four proven psychosocial therapies for smoking cessation have been validated in over 150 RCTs (Hughes 2003; The Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel et al. 2008). Third, controlled trials of nicotine dependence are very common; e.g. www.clinicaltrials.gov lists 689 controlled intervention trials on tobacco use.

The major purposes of the current article are a) to provide an overview of the ethical concerns about placebos and non-active controls and evaluate their applicability to RCTs of pharmacological and behavioral treatments for smoking cessation and b) to suggest methods that smoking cessation RCTs can use to mitigate such concerns. This article is not a comprehensive nor systematic review, does not provide a formal ethical analysis using ethical principles such as respect for persons, contracting principles, etc., and is not comprehensive. Many such reviews already exist (Emanuel & Miller 2001; Forster et al. 2001; US Food and Drug Administration. 2001; Huston & Peterson 2001; Weiss Roberts et al. 2001; Rothman 1994; Temple & Ellenberg 2000; Ellenberg & Temple 2000; Tollman 2001; Carpenter et al. 2003). The current paper's contribution is an examination of how these ethical concerns apply to smoking RCTs and a suggestion of methods to decrease these concerns. The paper is written from a scientist-clinician perspective and the conclusions of the paper are based on the author's subjective judgments.

## 2. Methods

### 2.1. Definition of Non-Active Conditions

Much of the literature focuses on the use of placebo pills and the term "placebo" has been used to describe behavioral non-active control conditions. The current review will, instead, use the phrase "non-active controls" to refer to attention-only, contact-only, known ineffective, no-treatment, placebo or wait-list conditions to emphasize that the ethical concerns apply to inert (or non-specific) behavioral conditions as well as inert pharmacological interventions. The review defines a "non-active" condition as one that the experimenter and the community of scientists and clinicians believe is not effective due to its specific contents.

### 2.2. Identification of Relevant Literature

I searched PubMed, Embase, and for PsychInfo using the words/stems "(smok* OR tobacco OR cigar* OR nicotin*) AND ethic*." This produced 329 citations but only one dealt with non-active groups in smoking cessation RCTs (Shelton 2001). A similar search for RCTs of alcohol and drug abuse RCTs using (alcohol* OR drug OR substance) AND ethic* AND (dependenc* OR cessation OR abuse) AND ethic produced 285 publications, none of which were relevant. Thus, I decided to collect review articles on the ethics of non-active conditions in RCTs of any disorder and examine how they apply to smoking cessation RCTs. To do this, I searched for "placebo*" or one of the synonyms for non-active conditions used in the Cochrane review on placebo effects(Hrobjartsson & Gotzsche 2007) and with "ethic*" in the abstract or title. I searched PubMed and PsychInfo and limited this to editorials, meta-analyses and reviews. This resulted in 236 citations that discussed placebo and behavioral non-active control conditions in studies of alcohol/drug abuse, mental disorders and physical disorders. I also examined what appeared to be relevant articles cited in the bibliographies of these reviews. I located many excellent articles on the ethical issues of using non-active controls in RCTs,

but none mentioned smoking cessation or alcohol/illicit drug abuse RCTs (Emanuel & Miller 2001; Forster et al. 2001; US Food and Drug Administration. 2001; Huston & Peterson 2001; Weiss Roberts et al. 2001; Rothman 1994; Temple & Ellenberg 2000; Ellenberg & Temple 2000; Tollman 2001); thus, the discussion below is based mostly on the author's attempt to apply discussions referring the ethics of non-active conditions in RCTs of alcoholism, depression, etc, to the ethics of such conditions in smoking cessation RCTs. At the end of the article, the author comments on the relevance to non-nicotine drug problems as well.

## 3. Results

### 3.1. Benefits of Non-Active Controls

Many articles have argued the scientific rationale for the inclusion of non-active controls (Emanuel & Miller 2001; Forster et al. 2001; US Food and Drug Administration. 2001; Huston & Peterson 2001; Weiss Roberts et al. 2001; Rothman 1994; Temple & Ellenberg 2000; Ellenberg & Temple 2000; Tollman 2001). One major argument for their inclusion is they control for natural remissions of a disorder. Given that many smokers quit without any treatment (The Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel et al. 2008), natural remissions of nicotine dependence are common.

A second argument is that, when a non-active condition is credible (e.g. a time-matched, face-valid behavioral treatment or a placebo), it can control for expectancies and determine whether improvement is due to the actual contents of the treatment and not to "non-specific factors" (O'Leary & Brokovec 1978). This second argument assumes that non-active controls improve outcomes. Many papers have stated that, among those with behavioral disorders, a minority (often cited as one-third) will improve with placebos. More specifically, because smoking can be influenced by expectancy (Mooney et al. 2004), many have assumed that placebos increase smoking cessation. However, a recent empirical review has challenged the notion that placebos improve outcomes of several conditions (Hrobjartsson & Gotzsche 2001). This review identified nine smoking cessation RCTs that included both a placebo and a true no-treatment condition (Hrobjartsson & Gotzsche 2001). The placebo condition had a numerically greater rate of abstinence in only one of the nine trials. Thus, surprisingly, whether placebos are actually active in smoking cessation RCTs is unclear.

In fact, one could argue that not using non-active controls can itself cause harm. This is because the methods and designs to avoid non-active controls each have drawbacks (see below). For example, assume a new treatment is compared to standard treatment without a non-active condition. Then assume that the new treatment produces a lower quit rate than standard treatment and thus, the experimenter concludes the new treatment should not be pursued. But then assume that actually the new treatment still shows superior efficacy to non-active controls, is inexpensive, is very easy to use and has fewer adverse events than standard treatment. In this scenario, the new treatment is still worthwhile. Thus, here the failure to use a non-active control caused abandonment of a treatment that could have helped millions of those with smoking or alcohol/illicit drug problems..

### 3.2. Ethical Liabilities of Non-Active Conditions

**3.2.1. Deprivation of Known Effective Treatments—**One concern is the deprivation of a smoker of an available, known effective treatment. This concern is typically raised in the context of a patient-clinician relationship in which there is an expectancy that the clinician has a duty to provide treatment to the smoker. This would be the case in which physicians, counselors, etc enter their own patients/clients in a RCT. However, most often in smoking cessation trials neither the experimenter, nor the smoker, have met before and many trials are

run in a non-clinical setting. Whether an experimenter has a duty to provide participants in a research trial with the best available treatment is debatable. Smokers may expect that experimenters are acting as if they were clinicians. For example, many studies have documented a "therapeutic misperception" in which, despite clear information otherwise, participants in trials persist in mistakenly believing that the experimenter would not allow the participant to receive anything less than optimal treatment (Miller & Joffe 2006; Appelbaum & Lidz 2006).

**3.2.2. Harm from Deprivation of Treatment—**The World Health Organization's revision of the Helsinki declaration states that, even if treatment is not provided, this could still be ethical as long as participants "will not be subject to any additional risk of serious or irreversible harm "(Forster et al. 2001). Smokers in non-active controls should have a greater chance of failing than if they obtained optimal care. One could hypothesize that the increased failure during the study discourages smokers and decreases the probability of latter attempts and, thereby, of eventually quitting. This review could not locate a direct empirical test of this hypothesized risk. One study did report that 46% of those who received an active treatment and failed to quit, attempted to quit again in the next 6 mo (Spanier et al. 1996). This rate is actually higher than the population average for a 6 month period (US Center for Disease Control 2006). Adequate direct empirical tests of whether failure to quit after treatment suppresses or delay future quit attempts are sorely needed.

### 3.3. Factors That May Mitigate the Harm of Assignment to a Non-Active Group

One possible mitigating factor in the potential harm from assignment to a non-active condition is whether the condition can be cured without treatment. For example, failure to treat Hodgkin's lymphoma could be seen as unethical because spontaneous remission without treatment is rare. In contrast, "self-cures" with smoking cessation are possible and, in fact, are the majority of successes (West 2005). Thus, one could argue that deprivation of treatment is less harmful with smoking cessation than with disorders in which self-cures are not possible.

Another mitigating factor is the magnitude of the efficacy of proven treatments that is being foregone. Foregoing a treatment with a 5% success rate vs. foregoing a treatment with a 95% success rate, has different ethical implications. Whether smoking cessation treatments provide small or large treatment effects is debatable and depends on the treatment foregone. For example, brief counseling typically increases quit rates by < 5% whereas optimal combination of medication and counseling increases quit rates by 20–30% (The Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel et al. 2008).

Another possible mitigating factor is the availability of treatment. If most persons with the disorder do not receive treatment, then depriving them of a treatment could be considered less harmful than if almost all with the disorder received treatment. About one-third of smokers receive treatment when they quit; thus, not receiving treatment is the norm (Shiffman et al. 2008). Also, usually smokers have to pay out of pocket for treatment (Nissen et al. 2008), whereas treatment provided in a RCT is usually free. Although there are no empirical data, the author's anecdotal experience is that many of those who volunteer for smoking cessation RCTs do so because the treatment is free. They are essentially stating that they are willing to accept the risk of being assigned to a less-than-optimal treatment in return for not having to pay for treatment.

### 3.4. Methods to Mitigate Possible Harm From a Non-Active Control (Table 1)

**3.4.1. Provide more explicit information in consent—**One way to possibly mitigate harm is to make the issue in the informed consent more explicit. For example, consents usually state something like "you can leave the study at any point, without prejudice." Many

participants believe that they "should" remain with the study, even if doing poorly (Forman et al. 2002). Thus, the consent process could more explicitly and emphatically state something like "If you ever believe that you are not benefiting from the treatment in our study or that you would benefit from a treatment that you are not receiving as part of our study, you should discuss with us whether it would be in your best interest to obtain that treatment" and be followed by a clear statement about how this would influence continuation in the trial. Also, the consent process could also explicitly state the possible harm of being assigned to a non-active control group; i.e., that this might discourage a later quit attempt.

**3.4.2. Recruit only treatment-resistant smokers—**Another method is to enter only smokers who have failed all possible proven treatments or, at least, all treatments they are willing to try. Since these smokers have not responded to active treatment, one could argue that assigning them to a non-active rather than active treatment is ethical. Although this would decrease the generalizability of the study somewhat, most, smokers who try new smoking cessation treatments have failed prior treatments (Shiffman et al. 2005). In addition, one could argue this is the population of smokers most likely to use the new treatment when marketed. The major limitation of this strategy is that, such smokers may be resistant to any therapy and this could decrease the sensitivity of the experimental test of a new medication.

**3.4.3. Provide treatment in a different modality—**Another method is to provide treatment of a different modality in the control group. Many studies of smoking cessation medications provide empirically-validated behavioral treatment to those in the placebo group and many RCTs of behavioral treatments provide empirically-validated medication to those in the non-active behavioral group. In these cases, one can argue, that although smokers in the non-active group may not receive the optimal treatment (i.e., combined medication and behavioral therapy), they are receiving a proven treatment. Provision of behavioral therapy does not appear to decrease the sensitivity to detect active vs. placebo medication differences (Silagy et al. 2004) but whether provision of medication influences the ability to detect active vs. nonactive psychosocial therapy is less clear (Stead et al. 2006).

**3.4.4. Test new treatment as an add-on—**One alternative to non-active controls is to test the new treatment as an add-on to an existing proven treatment; thus, even in the control condition, smokers receive a proven treatment. A possible problem with this procedure is that it may decrease the sensitivity of the test of the new treatment. For example, many studies have found that nortriptyline and bupropion outperform placebo when given alone; however, existing studies have not found that nortriptyline and bupropion outperform placebo when added to nicotine patch treatment (Hughes et al. 2007). Similarly, behavior therapies have been shown more efficacious than no treatment when given alone have often not been found more efficacious when added to NRT (Lancaster & Stead 2005). Another problem is that the add-on experimental test does not replicate the way the medication or behavioral treatment may be marketed or used; i.e., as an effective treatment when given alone.

**3.4.5. Use a Dose-Response Design—**Another alternative to non-active controls is to conduct a dose-response study in which all smokers receive an active dose of the treatment. In this design, demonstration of dose effects is used to impute efficacy. Interestingly, the ethics of this design depends on the investigator's a priori expectation for the lowest dose. For example, in one nicotine gum trial, a dose of 1 mg was given and the experimenter clearly expected this dose to be inactive (Jarvis et al. 1982). On the other hand, many behavioral therapy studies have compared a minimal treatment that the experimenter thought was active with a more intensive treatment (Lancaster & Stead 2005; Stead & Lancaster 2005).

**3.4.6. Use unequal randomization—**Another alternative is to use unequal randomization such that fewer participants are randomized to the non-active group that to the new treatment. This design does decrease power somewhat but assists with recruitment as participants can be told they have a > 50% chance of receiving the new treatment.

**3.4.7. Use stopping rules—**Another alternative is to use stopping rules to stop a trial as soon as it is clear that the new treatment is or is not active. (Schulz & Grimes 2005) This would prevent some participants from being exposed to a non-active treatment when their results are not necessary to make a decision about the efficacy of a new treatment. The liability of this procedure is that it requires an adjustment in the p value and decreases the statistical power of a study (Schulz & Grimes 2005).

**3.4.8. Use other designs—**Some have proposed that trial designs with non-active conditions be abandoned in behavioral treatment research and suggested alternative designs (Borkovec & Sibrava 2005). They suggest dismantling designs to compare a complete behavioral treatment with another a treatment identical except it is missing one component. This would determine if the component is active. They also suggest catalytic designs which test whether a treatment component facilitates (i.e. interacts) to make the treatment effective; e.g., perhaps self-monitoring catalyzes stimulus control treatments. Wait-list controls are often used in treatment studies. Their problem is that smokers may lose motivation to quit over time and, thus, a wait list could result in fewer quit attempts. One other somewhat less-satisfactory alternative is to use historical controls. For example, in the Cochrane meta-analyses the smallest lower boundary of the 95% confidence intervals for the odds ratios for medications for smoking cessation is 1.7 (for nicotine gum) (Silagy et al. 2004). Thus, for example, one could argue that if one found that the lower bound of the 95% CI for the OR of a new treatment vs. placebo was > 1.7, the new medication is likely to be as effective as nicotine gum and, thus, it is not necessary to have a non-active condition. Such historical comparison could be improved by selecting only those historical trials that are similar in subject entry criteria, setting, etc to the new treatment RCT. Given the plethora of NRT studies this may be feasible. However, even if this is done, one can never be sure the results of historical controls are identical to those of current non-active controls. For example, one analysis found the success rates of placebo controls has substantially declined over time (Irvin et al. 2003).

**3.4.9. Provide optimal therapy to those who fail during study—**Another method to abate possible harm is to have a priori specified criteria for treatment failure; then take participants who have failed and treat them with the standard or optimal treatment in a non-research setting. Although some trials have done this, the feasibility and benefit of this procedure has not been described in the published literature. As described above, the little evidence about motivation to quit smoking after a quit attempt, suggests many failed smokers would be willing to try again (Spanier et al. 1996). One variation is to treat all failures and the other is to treat only those that fail in the non-active group. However, in double-blind studies, doing the latter as soon as the participant fails (i.e. during the study) requires breaking the blind. Another alternative is to treat all failures only after the study ends; however, given many studies take years to complete, this is less likely to reverse any harm from the non-active group.

**3.4.10. Use Non-Inferiority Trials—**One alternative to RCTs with non-active controls are RCTS of new vs. standard treatment that aim to show the new treatment is as good as a proven standard treatment; i.e., equivalence or, perhaps more accurately, “non-inferiority” trials (Temple & Ellenberg 2000; Ellenberg & Temple 2000). One issue in these trials is whether the “standard treatment” should be usual care or optimal care. Usual care can be defined empirically by surveys of what the typical person with the disorder receives. With smoking the most common treatment is brief advice from a physician (Cokkinides et al. 2005) which,

given it only increases quitting by < 5%, would be easy to out-perform. Optimal care can be defined as the consensus across formal guidelines or recommendations. The USPHS, UK and other guidelines recommend all smokers receive both advice to quit, first-line medication and maximally-acceptable psychosocial therapy (The Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel et al. 2008; West et al. 2000). This would produce a quit rate of about 20% (check UK guidelines).

One possible problem with non-inferiority trials is that they assume that, within the RCT of the new treatment, the standard treatment is active (i.e. induces more abstinence than a non-active control). In some areas (e.g. depression), well-accepted treatments are not active in one-third to half of trials (Temple & Ellenberg 2000). Whether it is safe to assume all smoking medications are active when used as a comparator to a new treatment can be assessed by two sets of data. First, in RCTs of their own efficacy, proven medications for smoking cessation very reliably increase quitting in RCTs. For example, NRT was effective (OR > 1.2) in 104/109 (93%) trials (Silagy et al. 2004) and bupropion in 30/32 (94%) trials (Hughes et al. 2007) (although this could be due somewhat to publication bias). Second, the author located eleven non-inferiority trials comparing a new treatment vs standard treatment vs placebo, and thus allowed a test of whether standard medication was still effective (i.e. outperformed placebo). All seven of the comparator studies in which bupropion was the standard medication, bupropion outperformed control (i.e. OR > 1.2) (Nides et al. 2006; Jorenby et al. 2006; Gonzales et al. 2006; Haggstram et al. 2006; Hall et al. 2002; Wagena et al. 2005; Piper et al. 2007). In four studies of NRT as a comparator, NRT did outperformed placebo in two studies (Rose et al. 1998; Uyar et al. 2007), did not do so in one study (Jensen et al. 1991) and outperformed placebo on some, but not all, measures in a fourth study (Jorenby et al. 1999).

An important issue in active vs. standard trials is the definition of “non-inferiority.” These trials typically define “non-inferiority” as obtaining an outcome with the new treatment whose lower 95% confidence interval does not include an outcome that is worse- “to a clinically significant degree” – than the standard treatment (Temple & Ellenberg 2000). So, for example, assume in a new vs standard RCT of a cancer, the new treatment produces a remission rate of 30% for a cancer and standard treatment produces a rate of 20%. If the sample size was such that the lower bound of the 95% CI for the new treatment was 18% (i.e., only 2% worse than standard treatment), most clinicians would say that it’s unlikely the new treatment is worse “to a clinically significant degree” than the standard treatment. However, if the sample size were smaller and the lower bound of the 95% CI was 10% (i.e., 10% worse), then clinicians might state that even though the new treatment looks more efficacious, there is still a reasonable chance it might be worse “to a clinically significant degree” than standard treatment. Many have declared very small differences (e.g. a difference of 1% in quit rates) to be clinically significant (West 2007). Thus, in order for a treatment to have a lower 95% CI that is not 1% less than standard treatment, it would likely have to have a much larger quit rate than the standard treatment (i.e. essentially showing superiority vs. standard treatment) or have an extremely large sample size.

Another potential problem with new vs. standard RCTs is that methodological features such as selection criteria, experimental design and outcome measures can bias the study. For example, perhaps the RCT of the new treatment attracted mostly those that did not respond to the standard treatment in the past. But even more problematically, poor experimental techniques in the new RCT increase the variability of outcomes and thereby increase the chance of finding the desired outcome of no difference between active vs. standard differences. This is clearly not an optimal situation. Optimal methods for non-inferiority trials have been explicated in a CONSORT report (Piaggio et al. 2006).

A final issue with new vs active comparisons is that they do not accommodate the possibility that new treatments may have efficacy greater than the non-active control but less than existing treatments but the treatment is still worthwhile. For example, assume a vaccine for the treatment of smoking is more effective than the non-active control but is inferior to varenicline. It could be that some smokers who are not willing to use varenicline are willing to use a vaccine (because it is not psychoactive or because they do not have to take pills every day for months) and thus having the vaccine available is worthwhile.

A common alternate to the two group (new vs standard treatment) equivalence design is to use a three group design of new treatment vs standard treatment vs no treatment (Temple & Ellenberg 2000; Ellenberg & Temple 2000). The major benefit of this design is that one can verify that the standard treatment is active plus one can both show that the new treatment is efficacious, even if it is inferior to standard treatment. The major liability is that the sample size is increased by one third.

## 4. Discussion

### 4.1. Research Recommendations

Many of the questions posed above are researchable (Table 2). Perhaps the most important question is whether assignment to a non-active condition with its increased failure rate undermines later attempts to quit. To test this, one could compare the incidence of future quit attempts or long term point prevalence abstinence outcomes among a) smokers who enter a trial, were assigned to a non-active condition and relapsed during the short duration of the study vs b) smokers who entered and who were assigned to active condition and relapsed or vs c) smokers who applied but were not-entered for reasons unrelated or minimally related to abstinence success or vs d) smokers who were trying to quit but did not apply for the trial. Clearly, there are selection biases in these groups that would need to be considered and controlled via covariates to as great an extent as possible in these analyses. Also, a better understanding of why smokers volunteer for smoking cessation trials and whether the therapeutic misperception applies to smoking research are needed.

## 5. Significance

Whether use of non-active conditions in smoking cessation trials is unethical is currently unclear. Even if assignment to a non-active treatment were shown to be harmful, it may still be possible to conduct ethical research with non-active conditions if certain conditions were met (Table 2). Use of only smokers who have failed optimal treatment and immediate treatment of failures with optimal treatment are perhaps the most important possible conditions. The use of non-inferiority trials as alternatives to RCTs of new vs non-active conditions is problematic in smoking research because, given the huge public health impact of smoking, even a small amount of possible inferiority could be grounds for not using the new treatment.

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**Table 1**

Actions That Could Mitigate Possible Harm From Use of a Non-Active Control Group

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|---|
| Explicit instructions that this is not a therapeutic setting and that participants may receive less than optimal treatment, |
| Enter only smokers who have failed optimal treatment |
| Provide treatment of a different modality in the control group |
| Test new treatment as add-on to standard treatment |
| Assess efficacy by dose-response test |
| Use unequal randomization |
| Use stopping rules |
| Provide those who fail with a free optimal treatment in a reasonable time frame |
| Switch to an active vs standard comparison |

**Table 2**

Researchable Questions About The Ethics of Using Non-Active Conditions

| |
|---|
| Do placebos or non-specific behavioral conditions increase cessation vs. no-treatment? If so, what is the behavioral mechanism of this effect? |
| Does the “therapeutic misperception” apply to smoking cessation trials set in non-medical settings? |
| Does trying to stop smoking and failing increase or decrease the probability of or time to another quit attempt? Does this vary depending on whether the smoker received a known active treatment, a known non-active treatment, or did not know what they received? |
| Why do smokers enter trials; e.g.,, to obtain free treatment, because they believe the treatment will be effective for them, because they have already failed all treatments that they are interested in, treatment in a trial is superior, because they believe the monitoring, expectancies, structure or adjunctive treatment is helpful or to help advance science? |
| What is the treatment history of most smokers than enter cessation trials; e.g., have most already received optimal treatment? |
| How well do smokers in a trial understand the disadvantages of being in a non-active treatment, that they can leave the trial and seek treatment elsewhere, etc? |
| Is it more difficult to show new treatment vs. non-active control efficacy in a sample of re smokers who have failed optimal therapy in the past, in an add-on study in which all smokers receive NRT and behavioral counseling? |
| If all smokers who fail are offered treatment immediately, how many pursue this option? Does having this option undermine motivation to stop during the study in smokers who know or believe they are in a non-active condition? |
| How often do well-accepted, previously-validated behavioral and pharmacological treatments fail to outperform non-active treatments (and thus lose their ability to serve as a comparator to new treatments)? Does this differ among those who have vs. have not received this treatment in the past. |
| What would most clinicians accept as showing non-inferiority; e.g. would numerical superiority with a lower 95% CI that is below the mean of the standard treatment acceptable? |
| Would clinicians believe that demonstration that a new treatment had efficacy vs. placebo but inferiority to standard therapy be useful a) because marketing of the new treatment may prompt some smokers to try to quit or b) because there may be some smokers who respond only to this new treatment? |