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**School of Psychology **

**Title:** The Role of Awareness in Withdrawal Symptoms during

a Nicotine-Patch Tapered Dose-Reduction Regimen.

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**CONTENTS**

TITLE PAGE…………………………………………………………………………. 1

CONTACTS LIST……………………………………………………………………. 2

CONTENTS…………………………………………………………………………... 3

SUMMARY…………………………………………………………………………... 5

1. INTRODUCTION……………………………………………………………. 6

1.1 BACKGROUND……………………………………………………... 6

1.2 RATIONALE………………………………………………..………. 11

1.3 STUDY HYPOTHESES…………………………………………….. 11

2. STUDY OBJECTIVES………………………………………………….…... 11

2.1 OBJECTIVES….…………………………………………………...... 11

2.2 ENDPOINT………………………………………………………….. 12

3. STUDY DESIGN……………………………………………………………. 13

4. STUDY POPULATION…………………………………………………….. 13

4.1 NUMBER OF PARTICIPANTS…………………………………….. 14

4.2 ELIGIBILITY CRITERIA…………………………………………... 14

5. PROCEDURE………………………………………………………………... 14

5.1 PARTICIPANT SELECTION……………………………………...... 14

5.2 ENROLMENT/SCREENING/BASELINE SESSION………………. 15

5.3 MATERIALS………………………………………………………... 16

5.4 BASELINE MEASURES…………………………………………… 17

5.5 RANDOM ALLOCATION…………………………………………. 17

5.6 SUBSEQUENT VISITS…………………………………………….. 18

5.7 FOLLOW-UP………………………………………………………... 20

6. INVESTIGATIONAL PRODUCTS REQUESTED………………………... 20

6.1 STUDY DRUG……………………………………………………… 20

6.2 PLACEBO PATCHES………………………………………………. 21

6.3 DOSING REGIME………………………………………………….. 21

6.4 RATIONALE FOR STARTING DOSE…………………………….. 22

6.5 SUPPORT REQUESTED FROM GSK……………………………... 22

6.6 DOSE CHANGES…………………………………………………... 23

6.7 COMPLIANCE……………………………………………………… 23

6.8 OVERDOSE………………………………………………………… 23

6.9 PRIOR AND CONCOMITANT MEDICATIONS…………………. 23

7. STUDY ASSESSMENTS…………………………………………………… 23

7.1 PRELIMINARY SCREENING QUESTIONNAIRE……………….. 23

7.2 SCREENING AND BASELINE SESSION………………………… 24

7.3 MID-STUDY MEASURES…………………………………………. 25

7.4 DEBRIEF SESSION………………………………………………… 25

7.5 FOLLOW-UP……………………………………………………….. 25

8. DATA COLLECTION………………………………………………………. 25

9. STATISTICS AND DATA ANALYSIS……………………………………. 26

9.1 SAMPLE SIZE CALCULATION…………………………………... 26

9.2 PROPOSED ANALYSES…………………………………………... 26

10. ADVERSE EVENTS……………………………………………………….. 26

10.1 DEFINITIONS……………………………………………………… 27

10.2 DETECTING AEs AND SAEs……………………………………… 27

10.3 RECORDING AEs AND SAEs……………………………………... 28

10.4 EVALUATION OF AEs AND SAEs……………………………….. 28

10.5 REPORTING OF SAEs/SARs/USARs……………………………... 30

10.6 FOLLOW-UP PROCEDURES……………………………………… 30

11. PREGNANCY………………………………………………………………. 30

12. MONITORING AND QUALITY ASSURANCE………………………….. 31

12.1 PROJECT MANAGEMENT GROUP………………………………. 31

12.2 RISK ASSESSMENT……………………………………………….. 31

13. GOOD CLINICAL PRACTICE MODULE………………………………… 32

13.1 ETHICAL CONDUCT OF THE STUDY…………………………... 32

13.2 INVESTIGATOR RESPONSIBILITIES…………………………… 32

14. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS…. 36

14.1 AUTHORSHIP POLICY……………………………………………. 36

14.2 PUBLICATION……………………………………………………... 36

15 REFERENCES……………………………………………………………… 37

Appendix A – Study Questionnaires………………………………………… 41

Appendix B – Participant Information Statement…………………………… 56

Appendix C – Participant Consent Form……………………………………. 60

Appendix D – Debrief Statement……………………………………………. 61

Appendix E – Ad for General Population…………………………………… 63

Appendix F – Ad for University Students…………………………………… 64

Appendix G – Instruction Pack……………………………………………… 65

Appendix H – Timelines for Study (Procedure and Milestones)……………. 75

Appendix I – Study Design………………………………………………….. 77

**SUMMARY/PREFACE**

The expectancies, both positive and negative, that individuals hold about the likely effects of an upcoming treatment can significantly influence the outcome of that treatment. These expectancies can either be induced verbally by health professionals or can be formed through repeated exposure to the treatment over time. For many types of treatments a proportion of the total response to that treatment is an expectancy-induced response. We propose that individuals who are addicted to a drug come to expect withdrawal symptoms when they are aware of the upcoming discontinuation or reduction in dose of their drug of choice, and that this contributes to overall withdrawals over and above the physiological withdrawals that come from the absence of the drug to which they are addicted. Following on from this, we propose that, for individuals on a tapered nicotine-patch dose-reduction regimen, removing the knowledge of dose reductions will remove the expectancy-induced component of total withdrawal symptoms. One-hundred and forty participants will be placed on a 28-day nicotine-patch tapered dose-reduction regimen and will be tested daily for self-reported withdrawal symptoms and relapse rates. There will be two groups: Aware and Unaware. The Aware group’s patches will indicate accurately when dose-reductions occur. The Unaware group will be led to believe that they are remaining on the same dose for the entire 28 days. It is hypothesised that the Unaware group—who will not be aware of dose reductions and thus will not have an opportunity to generate an expectancy of withdrawal symptoms—will experience significantly lower withdrawal symptoms and rates of relapse across the study compared to the Aware group.

This study proposal has been created in order to request assistance from GSKCH for the supply of nicotine patches. We believe the study will shed light on some of the psychological processes that hinder attempts to quit smoking and serve as a preliminary model for future interventions. It is crucial for the success of the study that placebo nicotine patches be indistinguishable from active patches, in all aspects including size, shape, feel, weight and on-patch labels. As GSKCH has used and supplied matched placebo patches in the past, they are in a unique position to assist this study. GSKCH’s contribution will be acknowledged in all publications and presentations resulting from this research.

*Authors Note: in the following proposal, the terms expectancy-induced withdrawals and placebo-withdrawals are used interchangeably.*

**1. INTRODUCTION**

**1.1 BACKGROUND**

**1.1.1 Expectancy-induced treatment effects**

It is well established that the expectancies and beliefs that a patient holds concerning a treatment can influence the effectiveness of that treatment. This phenomenon, known as the placebo effect, can mimic, enhance or ameliorate the effects of the active treatment itself, depending on whether the expected effects are positive or negative. For years the placebo effect has been considered a nuisance, an artefact to be ‘controlled out’ in order to determine the effects of the active treatment alone. However recent advances in placebo research suggest that patients’ expectations of treatment effects, far from being a nuisance, can in fact be harnessed in order to enhance treatment outcomes.

Placebo effects, also known as expectancy-induced effects, have been observed for a wide range of phenomena, including analgesia (Amanzio & Benedetti, 1999; Tang & Colagiuri, 2013), improved motor function (Pollo et al. 2002), reduced insomnia (Colagiuri, McGuiness, Boakes & Butow, 2012; Suetsugi, Muzuki, Yamamoto, Uchida, & Watanabe, 2007), bronchioconstriction (Butler & Steptoe, 1986) and immunosuppression (Bovbjerg, Ader, & Cohen, 1984). Drugs of abuse also show expectancy effects. For example placebo administration of alcohol (Fillmore, Carscadden, & Vogel-Sprott, 1998), THC (Kirk, Doty, & deWit, 1998), caffeine (Lotshaw, Bradley, & Brooks, 1996), and d-Amphetamine (Mitchell, Laurent, & de Wit, 1996), can cause both subjective and objective effects that mimic the effects of the drugs themselves.

Expectancies can apply to aversive effects as well as desired effects. For example in a trial testing treatment of unstable angina with aspirin, simply listing gastrointestinal irritation as a side-effect on one group of participants’ consent forms caused that group to report significantly higher rates of this side-effect than another group whose consent forms made no reference to it (Myers, Cairns, & Singer, 1987). Similarly participants given muscle relaxants who were told it was a stimulant reported greater muscle tension than those told truthfully that it was a relaxant (Flaten, Simonson, & Olsen, 1999) and participants with food allergies who were told that a saline injection was an allergen developed allergic symptoms (Jewett, Fein, & Greenberg, 1990). Luparello, Lyon, Bleecker and McFadden (1969) gave asthmatic patients nebulised saline to inhale and told them it was an allergen. Approximately half of all participants developed dyspnea, decreased vital capacity, and increased airway resistance. Possibly the most well-known example of an aversive expectancy-induced effect (or nocebo effect) is the anticipatory nausea experienced by patients undergoing chemotherapy (Montgomery & Bovbjerg, 2001; Roscoe, Hickock and Morrow, 2000).

Sometimes aversive and desired expectancy-induced effects can result from the same treatment. For example Colagiuri, McGuiness, Boakes, and Butow (2012) found that giving participants experiencing sleep difficulties a placebo in the guise of a hypnotic resulted in a reduction in global sleep-difficulty and an increase in total sleep per night compared to no-treatment controls. However when this placebo pill came with a warning of either a significant increase or decrease in appetite as a possible side-effect, it caused participants to report this side-effect, in the direction suggested by researchers, at a significantly higher rate than participants who had received no such warning.

**1.1.2 Expectancy and Withdrawal**

The effect that expectancies have on patient outcomes has been examined for a vast array of treatments and symptoms. One question, however, that has received little attention is that of withdrawal symptoms. Withdrawal symptoms are a cluster of mostly aversive physical and psychological symptoms that occur upon discontinuation or reduction in dose of a substance that has come to be relied upon for maintaining affective, cognitive, and physiological equilibrium. Withdrawal symptoms are a significant predictor of relapse to smoking (West, Hajek, & Belcher, 1989; Piasecki et al. 2000; Shiffman et al. 1997a; Killen & Fortmann 1997; Patten & Martin. 1996). Physical withdrawal symptoms include decreased adrenaline, cortisol, heart rate, orthostasis, thyroid function and tremor as well as increased taste for sweets, metabolic rate, weight and slowing of the EEG. Psychological symptoms include anxiety, craving for cigarettes, depression, irritability, restlessness, difficulty concentrating, hunger and nocturnal awakenings. These symptoms are highly reproducible, observable by others, and can be clinically significant (Hughes, 1992a; Hughes & Hatsukami, 1987). Cravings for cigarettes are generally held to be the most salient of the nicotine withdrawal symptoms and the most significant predictors of relapse (West & Schneider, 1987; Russell, 1988) and can continue up to 6 months after the acute physical symptoms have disappeared (Hughes et al., 1994).

Given that many of the effects of drugs of abuse have been shown to be sensitive to expectancy manipulations and that expectancies can be formed around aversive as well as desired symptoms, there is no *a priori* reason why, over time, withdrawal symptoms could not also become subject to expectancy effects. In support of this is evidence that withdrawal symptoms can be induced by the cues that have been associated with those symptoms in the past, and by these cues alone, even when participants are not in a current state of withdrawal prior to the presentation of these cues (Valliant, 1988; Kenny et al. 2006; Dole & Nyswander, 1965).

**1.1.3 Drug Replacement Therapies**

Drug replacement therapies involve the controlled administration of either an agonist of a drug or the drug itself but in a different form. Examples of drug replacement therapies include heroin addicts being given methadone or buprenorphine (both opiate agonists) orally to replace injection of heroin and nicotine addicts being given nicotine in the form of gum, patches or nasal spray to replace smoking cigarettes. Drug replacement therapies allow the patient to focus on coping with the sudden discontinuation of the habitual behaviours, emotions, and cognitions surrounding their drug dependence without having to deal with the physical withdrawal symptoms. Transdermal nicotine patches, for example, have been shown to be more effective at achieving lasting smoking cessation than ‘cold turkey’ attempts (Stapleton et al.1995; Shiffman, Ferguson, Gwaltney, Balabanis, & Shadel, 2006). When a stable maintenance dose has been achieved the patient can either discontinue use of the replacement therapy completely, which once again is likely to induce a withdrawal response, or undergo a tapered dose-reduction regimen. Tapered dose-reduction regimens involve the initial dose of the drug-replacement vehicle being reduced gradually in discrete stages down to a zero dose.

**1.1.4 Expectancy and Nicotine**

Several studies using a balanced-placebo design—a more powerful design for separating expectancy effects from active effects than the traditional placebo-controlled design (Rohsenow & Marlatt, 1981)—have shown that beliefs and expectancies about nicotine can influence therapeutic outcome. Juliano and Brandon (2002) assessed the effects of nicotine and instructional set on anxiety reduction in smokers given either regular nicotinised or de-nicotinised cigarettes. They found that, in abstinent smokers given cigarettes or de-nicotinised cigarettes, being instructed that their cigarette contained nicotine produced a pronounced anxiolytic effect in participants who believed that nicotine reduced anxiety, whereas participants who did not hold this belief experienced no reduction in anxiety. In addition they found that urge to smoke/cravings were significantly lower in the group who were told they had smoked a nicotinised cigarette, regardless of whether they had actually smoked one or not. Dar, Stronguin and Etter (2005) also used a balanced placebo design to measuring whether participants’ expectancies affected the extent to which nicotine gum, patches or inhaler reduced cigarette consumption. They found that participants who believed they had received active treatment had larger reductions in cigarette consumption than those who believed they had received placebo, regardless of whether they had received active treatment or not. Gottlieb, Killen, Marlatt and Taylor, (1987) found, using a balanced placebo design, that expectation of receiving nicotine gum predicted significant decreases in physical symptoms and less smoking in the first week after quitting, and that, compared with the effects of expectancy, the *actual* gum that subjects received, either nicotine or placebo, seemed to have no effect on either withdrawal symptoms or smoking behaviour. Using a standard placebo-controlled design, Bailey, Fong, Bryson, Fortmann, and Killen (2010) compared the assignment beliefs of those participants in a nicotine-patch tapered dose-reduction regimen with a group receiving equivalent placebo patches and found that those who believed they had received active treatment avoided relapse for longer than those who believed they had received placebo, regardless of actual assignment condition. Worthy of note is that: a) both groups that guessed placebo experienced faster time to relapse than the conditions that guessed active; b) the Active Guessed Placebo group experienced faster time to relapse than the Placebo Guessed Active, implying that beliefs have a greater effect on time to relapse than the type of treatment.

The results from the studies mentioned above suggest that the expectancy that a nicotine replacement therapy will ameliorate nicotine withdrawal symptoms is enough to produce a reduction in these withdrawal symptoms even in the absence of actual nicotine. The fact that withdrawal symptoms can be reduced a placebo, that is by expectancy alone, implies that a significant portion of the dynamics of drug withdrawal—the presence of symptoms following abstinence and their reduction following drug administration—is attributable to expectancies.

**1.1.5 Open/Hidden Designs**

Recent research into expectancy effects have sought alternative methods to the traditional double-blind or balanced-placebo designs to separate the effects of active treatment from the effect of expectancies. The open/hidden paradigm, for example, compares the efficacy of active treatment in a group of participants who know they are receiving the treatment with a group who receive the same treatment but who are unaware they are receiving it. The latter group thus are experiencing active treatment effects without any expectancy of receiving it, something that cannot be measured in a placebo-controlled trial (Benedetti, Carlino, & Pollo, 2011).

Benedetti et al. (2003) showed that self-reported postoperative pain increased less following interruption of morphine delivery in patients who were not informed about the interruption compared with those who were informed.If the increase in pain following interruption of morphine can be seen as a related phenomenon to the onset of withdrawal symptoms following the discontinuation or reduction of the normal dose of a drug in an addicted individual—both involve an expected increase in distress following deprivation of a relied-upon drug—then the finding of Benedetti et al. (2003) provides evidence consistent with the idea that overall withdrawal symptoms can be reduced by removing the expectancy of withdrawals[[1]](#footnote-1).

**1.1.6 Summary**

Results from Bailey et al. (2010) and from the balanced-placebo studies above, when combined with the findings from open/hidden designs such as Benedetti et al. (2003), provide support for the idea that removing expectancies of withdrawals could significantly reduce the total withdrawal response experienced by the addicted individual whose dose is reduced or discontinued.

If expectancies of changes in psychophysiological state—caused by the repeated pairings of environmental stimuli surrounding the administration of a drug with the drug’s pharmacological effects—are enough to cause placebo responses that mimic the acute effects of the drug, it also follows that repeated pairings of the stimulus surrounding discontinuation or reduction of a drug with the concomitant withdrawal symptoms could also produce expectancies that lead to placebo withdrawal responses. In long-term, dependent drug users, the environmental and/or verbal cues that indicate discontinuation or reduction of dose will have been paired many times in the past with aversive physical and psychological withdrawal symptoms. Thus any cues that indicate that such a discontinuation or reduction is about to take place should produce an expectancy of aversive withdrawal symptoms that may lead to concomitant placebo withdrawal response.

**1.2 RATIONALE FOR THE STUDY**

If a portion of the withdrawal symptoms experienced by an addicted individual on a tapered dose-reduction regimen are expectancy-induced withdrawals, brought about by the prior knowledge of impending dose-reductions, then, by corollary, removing the environmental and verbal cues that indicate that a dose-reduction is forthcoming should remove the expectancy-induced component of any subsequent withdrawal response.

Furthermore, if withdrawal symptoms, whether physical or psychological, relate directly to likelihood of relapse and if expectancy-induced withdrawal symptoms contribute to total perceived withdrawal symptoms over and above actual withdrawals, then any intervention that can minimise expectancy-induced withdrawal symptoms in patients on a dose-reduction regimen may help to reduce the likelihood of relapse.

**1.3 STUDY HYPOTHESES**

The study’s hypothesis is that abstinent smokers on a nicotine-patch tapered dose-reduction regimen who do not expect their dose to reduce and who are unaware of the timing and magnitude of dose-reductions, will report lower withdrawal symptoms, exhibit better treatment adherence (i.e. lower relapse rates) and have longer duration of post-study abstinence than individuals who are aware of the timing and magnitude of dose reductions. If this hypothesis is proven true it may provide evidence on which to base actual drug-replacement interventions in future, whereby smokers preparing to commence a nicotine-patch tapered dose-reduction regimen consent to being blinded to the timing and magnitude of dose reductions in order to reduce withdrawal symptoms.

**2. STUDY OBJECTIVES**

The study’s objective is to provide support for the theory that beliefs and expectancies about withdrawals contribute significantly to overall withdrawal symptoms over and above purely physiological withdrawals.

**2.1 OBJECTIVES**

**2.1.1 Primary Objective**

The primary objective of the study is to measure, in smokers on a nicotine-patch tapered dose-reduction regimen, the extent to which knowledge about the timing and magnitude of dose reductions influences both the experience of withdrawals and likelihood of abstinence following these dose reductions.

**2.1.2 Secondary Objective**

The secondary objective of the study is to test whether participants’ individual differences in pre-existing factors—such as level of dependence prior to entering the study and expectancies about the likelihood and severity of withdrawal symptoms following nicotine abstinence—influence the efficacy of nicotine-patch tapered dose reductions in reducing withdrawal symptoms.

**2.2 ENDPOINT**

**2.2.1 Primary Endpoint**

The primary endpoints during the study will be average daily self-reported withdrawal symptoms across each 7-day dosing period (see Appendix I), total number of cigarettes smoked each 7-day dosing period, and carbon monoxide meter readings taken every 7 days. Primary endpoints after the study has ended will be self-reports of duration of abstinence at 1-week, 1-month, and 3-months.

**2.2.2 Secondary Endpoint**

Secondary endpoints will be the results obtained for the four questionnaires at the baseline session.

**3. STUDY DESIGN**

The study will be a mixed design with two levels of the between-subjects independent variable Information (Aware and Unaware) and eight levels of the repeated-measures independent variable Time (i.e. measured at 1, 8, 15, 22, and 29 days during the study, and 7 days, 1 month and 3 months post-study).

In order to determine whether biohistorical or cognitive factors have any influence over the effectiveness of the manipulation in reducing withdrawal symptoms, three classification variables will be included as potential predictors in analysis: 1) Duration of Addiction (self-reported age of onset of smoking); Number of Cigarettes Smoked Per Day and; 3) Expectations of Withdrawals.

Dependent variables will be: a) average daily self-reported withdrawal symptoms, measured using an online, email or text message version of the 7-item Mood and Physical Symptoms Scale (MPSS; West & Hajek, 2004); b) total number of cigarettes smoked in each 7-day dose period, measured daily online by email or text message with one question asking participants the number of cigarettes smoked that day; c) weekly carbon monoxide readings verifying self-reported number of cigarettes smoked; d) time to relapse, measured at 1 week, 1 month and 3 months after the end of the study period. See Section 7 for a detailed list of study assessments.

To determine whether participants’ beliefs about their true dose reduction schedule, rather than treatment group per se, predicts any of the outcome variables, a Probing Questionnaire will administered on participants’ final visit to the Smoking Research Unit (see Appendix A.9). The binary response options in Question 4 of this questionnaire (i.e. thought ‘Dose remained the same across the 28 days’ vs thought ‘Dose was reduced over the 28 days’) will be treated as two levels of a classification variable Belief.

**4. STUDY POPULATION**

The population targeted in this study will be moderate smokers of either sex over 18 years of age. Participants will be asked to refrain from smoking cigarettes or e-cigarettes during the study.

**4.1 NUMBER OF PARTICIPANTS**

One-hundred and sixty participants will be recruited for this study. All testing will be conducted at the Smoking Research Centre at the Brain Mind and Research Institute with the recruitment and testing periods staggered so that not all participants are tested at the same time.

**4.2 ELIGIBILITY CRITERIA**

In order to be eligible for inclusion in the study participants must:

1. be ≥18 yrs-old
2. smoke ≥ 5 cigarettes per day
3. have daily access to the internet
4. have no prior history of cardiovascular disease, hypertension, diabetes, or renal impairment.
5. not be pregnant or breastfeeding
6. have no prior history of chronic dermatological disorders
7. have no prior history of moderate to severe allergies
8. not have been on nicotine replacement therapy of any kind in the 3 months prior to commencement of the study
9. not be a regular user of illegal drugs
10. not be currently suffering from a diagnosed mental disorder
11. have not received any therapy or drug used to aid in the cessation of smoking (eg. nicotine gum, Chantix®, hypnotherapy) for thirty days prior to being admitted to the study.
12. not participating in another clinical trial for an experimental drug for the thirty days prior to the study.

See Appendix A.2 for full list of exclusion criteria.

**5. PROCEDURE**

**5.1 PARTICIPANT SELECTION**

Potential participants will be recruited either from the general public, (via answering advertisements on notice boards, newspapers, online classifieds websites such as Gumtree or via the Sydney University Career Hub website) or from the Sydney University 1st-year Psychology student body (as part of the Sydney University Psychology Research Participation Scheme). The ad will ask for participants interested in taking part in a study looking at different ways of using nicotine patches to quit smoking (see Appendix E and F). When participants answer the ad they will be directed to an online screening questionnaire (see Appendix A) where they will be asked for basic demographic data such as age and gender and for number of cigarettes smoked per day. If participants meet initial eligibility criteria (i.e. ≥5 cigarettes smoked per day, ≥18 yrs-old, and in possession of a mobile phone or daily access to the internet) they will be emailed and asked to attend a screening and baseline and admission session. Participants deemed ineligible in the initial screening questionnaire will be notified by email or telephone.

**5.2 BASELINE SESSION**

**5.2.1 Screening**

At the baseline session participants will first be asked further screening questions to determine if they meet the remaining eligibility criteria (see items 4 to 11 in section 4.2 above, and Appendix A). In order to verify that they are regular smokers (criteria 2, section 4.2), and to serve as a baseline with which to compare future readings, Carbon Monoxide (CO) levels will be taken using a CO meter. A reading of 10 ppm or greater indicates recent smoking (Benowitz et al. 2002) and thus a reading of less than 10 ppm will be grounds for exclusion from the study.

**5.2.2 Reimbursement**

Participants will receive patches for free in return for taking part in the trial. Participants deemed eligible will be reimbursed $40 at the end of the study to assist with their travel expenses and the inconvenience of attending the Smoking Research Unit over the course of the study. Participants deemed ineligible following the screening questionnaire will be informed that they did not meet the criteria outlined for the study and reimbursed a lesser amount for out-of-pocket expenses for attending the single session.

**5.2.3 Consent, Study Restrictions, and Participant Information Statement**

If participants meet all eligibility criteria they will be given a Participant Information Statement and asked to sign a Participant Consent Form (in which they will be asked to consent to being contacted at 1 week, 1 month, and 3 months to complete a 2-min online follow-up questionnaire).

The participant information statement will contain the cover story that the study aims to investigate how different methods of administering nicotine patches affect rates of abstinence from smoking. Participants will be told that they may be assigned either to a tapered reduction condition, where the dose of nicotine is reduced steadily over the course of the 29-day trial or to a control condition where their dose remains the same for the entire duration of the study. On the Participant Information Statement participants will also be informed that it is a condition of entry to the study that they agree:

1. to completely abstain from tobacco or e-cigarettes for the duration of the study
2. to not commence any alternative form of smoking cessation treatment, either drug or therapy, during the course of the study
3. refrain from enrolling in another clinical trial for an experimental drug during the study
4. to refrain from regular use of all other psychoactive substances, illicit or legal, with the exception of caffeine and alcohol during the study.
5. To apply two patches per day as instructed in the Instruction Pack (see Appendix G).

**5.2.4 Materials**

Patches will be NicoDerm CQ® daily 24-h transdermal nicotine patches.

**5.2.5 Baseline Measures**

Following admission to the study, participants will be given four baseline questionnaires (see Appendix A). Level of dependence prior to entrance to the study will be ascertained at a baseline session using both the 6-item *Fagerström Test for Cigarette Dependence* (FTCD; Fagerström, 2012) and a *Tobacco History Questionnaire* developed by Hendricks and Leventhal (2013) to measure pre-existing differences in smoking behaviour such as number of cigarettes smoked each day, age of smoking onset etc. Carbon Monoxide (CO) meters will be used to verify extent of dependence (i.e. level of daily use prior to testing). Pre-existing expectancies surrounding abstinence, withdrawal and ease of quitting will be measured during the baseline session using two scales: a 13-item questionnaire comprised of the *Withdrawal* and *Optimistic Outcomes* subscales of the *Smoking Abstinence Questionnaire* (SAQ; Hendricks et al. 2011), and the 4-item *Thoughts About Abstinence* scale (TAA; Hall, Havassy, & Wasserman, 1990). Finally participants will be given an 8-item online questionnaire, comprised of a 7-item nicotine withdrawal questionnaire— the Mood and Physical Symptoms Scale (MPSS; West & Hajek, 2004)—and a question asking participants how many, if any, cigarettes they had smoked that day (Carbon Monoxide meters will be used to verify this every 7 days). This questionnaire will be completed in front of researchers at the baseline session—either on participants’ phones or on a computer at the Smoking Research Unit—to ensure participants are familiar with how to access and complete it. This questionnaire will be the primary dependent measure of the study, to be completed every day of the 29-day study period. Thus the first of these questionnaires will serve as a baseline measure (i.e. taken before abstinence has commenced) upon which subsequent reports of withdrawal symptoms, cravings, and smoking can be compared.

**5.2.6 Random Allocation**

Following baseline measuresparticipants will be randomised to experimental group using Research Randomizer, an online research randomisation engine supplied by the Social Psychology Network (<http://www.randomizer.org>).

Participants will be randomly allocated into two groups—Aware and Unaware. The Unaware group will be told that they have been allocated to the control condition and thus will remain on a combined dose of 21 mg per day for the duration of the study. The Aware group will be told that their dose is being titrated 7 mg every 7 days from a starting dose of 21 mg.

**5.2.7 Instructions to Participants Upon Leaving**

Following random allocation to treatment group participants will be:

1. shown how to apply their first patches by researchers and given instructions on how to apply and use the patches (see Appendix G.3). These instructions for use will be based on the recommendations contained in the User’s Guide for NicoDerm® CQ 24-h transdermal nicotine patches provided by GSK (see <http://www.nicodermcq.com/nicotine-patch/how-to-use>), with the exception of the instruction that patches can be worn for either 16 or 24 h (participants will be asked to wear patches for 24 h).
2. given an instruction pack containing study requirements, emergency contact information, information about applying the patches, dosing schedule etc. (see Appendix G)
3. given their first set of 12 nicotine patches to apply at home
4. asked to completely refrain from smoking for the duration of the study
5. asked to return at the same time in 7 days time to have two patches applied and to receive their next set of 12 patches.
6. asked to keep the plastic wrapping for each patch they use and to return it to researchers on the next visit, so that researchers can verify they used all 12 patches over the six days.

**5.3 STUDY METHOD**

**5.3.1 At-home Application of Patches**

Patches will be applied by experimenters on Day 1, 8, 15 and 22 of the study and will be self-applied by participants on all other days. Participants will wear two patches per day. Four types of patches will be used: 14-mg, 7-mg, 0-mg placebo patch identical to the 14-mg active patch, and 0-mg placebo patch identical to the 7-mg patch. Both Unaware and Aware groups will have the combined dose of their daily 24-h nicotine patches titrated by 7 mg on average every 7 days from 21 mg on day 1 via differing combinations of these four patches (see Appendix I). Though dose will be reduced on average every seven days, the exact duration between each dose titration will be different for each participant. For example a participant could spend 6 days on 21 mg, 8 days on 14 mg, 9 days on 7 mg and 5 days on placebo. Thus average titration period for this participant will be 7 days across the study.Patches will be labelled with both the strength of the patch and which day of the trial that patch should be used (e.g. ‘Day 5: 14 mg’). The Aware group will have labels containing accurate dosing information on their patch. The Unaware group’s labels will (falsely) indicate that their combined daily nicotine dose is remaining on a 21 mg across the course of the study.

**5.3.2 Subsequent Visits to the Smoking Research Unit**

Participants will be required to attend the Smoking Research Unit on days 8, 15 and 22 of the study, where they will:

1. have their CO levels read and the 12 wrappers for the preceding 6 days’ patches collected by researchers
2. be asked if they had any problems with either the daily online questionnaires or the patches themselves
3. be asked if they wore two patches on every day of the 6-day period between visits to the Smoking Research Unit
4. complete a questionnaire detailing frequency and amount of use of other drugs during the 7-day period
5. have their first two patches of the 7-day period applied by the researcher
6. be given the remaining 12 patches for the week
7. be asked to return in 7 days time.

The final patches of the study (i.e. the final two of the 12 patches given to participants on their 3rd visit) will have labels reading:

*“The last 6 days you have been on 0-mg placebo patches. Therefore you have been completely nicotine-free for a week. Please make one more visit to see the researchers tomorrow and then you will be finished with the study. We hope that you have enjoyed participating in the study and that it has been useful in your attempt to quit smoking. You will not be required to wear these final two patches.”*

**5.6.2 Final Debrief Session**

On day 29 participants will attend a final debriefing session where they will:

1. be given a short questionnaire probing them for possible knowledge about whether the dosing information on patch labels was accurate
2. be told the true dosing regimen (for participants in the Aware condition this will not be necessary, as their labels accurately reflected their true dose throughout the study).
3. be given a final CO reading
4. be asked to complete a final online withdrawal questionnaire.
5. be given a debrief statement outlining the true purpose, design and procedure of the study.
6. be asked if they are willing to answer complete brief questionnaires concerning their abstinence status in 1 week, 1 month, and 3 month’s time.

**5.6.3 Withdrawal Procedures**

Participants will be given the right to withdraw at any point from the study at their own request. In the event of a severe adverse reaction, participants will undergo a medical examination and will be withdrawn from the study. Investigators also reserve the right to withdraw participants who fail to follow instruction protocols such as abstaining from regular use of psychoactive drugs or regular smoking on the grounds that it may contaminate results from the study. Should this occur (e.g. either a verbal report of smoking or a CO reading of >10 ppm) participants will be told by researchers that they have been regretfully withdrawn from the study as their data will contaminate results but that this will not affect their relationship with either the experimenters or the university.

**5.6.4 Emergency Unblinding Procedure**

In the event of an emergency, the principal researcher and supervisor should be notified immediately to assess the situation. Unblinding will be performed by Mr Llew Mills (contact details listed on page 2 of this proposal).

**5.7 FOLLOW-UP**

The participants who agreed to follow up at the baseline session will be contacted by email or phone by researchers at 1 week, 1 month and 3 months from the debrief session, where they will be asked if they have remained abstinent in the intervening period since the study ended. If they answer no they will be asked to estimate when they began to smoke again and how many cigarettes a day they are currently smoking.

**6. INVESTIGATIONAL PRODUCTS REQUESTED**

**6.1 STUDY DRUG**

**6.1.1 Study Drug Identification**

Generic Name – Nicotine Patch - Transdermal

Trade Name – NicoDerm® CQ

Dosage Form – 14-mg, 7-mg, and 0-mg (placebo) 16-24 h transdermal nicotine patches. *(Note: Two types of Placebo patches will be required: one that is identical to the 14-mg patch and one that is identical to the 7-mg patch).*

**6.1.2 Study Drug Manufacturer**

**Alza Corp.**  
1900 Charleston Rd.  
PO Box 7210  
Mountain View, CA 94039-7210  
USA  
Phone: (650) 564-5000  
Fax: (650) 564-7070  
[http://www.alza.com](http://www.alza.com" \t "_blank)

**6.1.3 Study Drug Marketer**

GlaxoSmithKline Australia Pty. Ltd.

Consumer Healthcare Division

82 Hughes Avenue, Ermington NSW 2115, Australia

Tel       +61296840269

Fax +61296841018

<http://www.gsk.com.au>

**6.1.4 Labelling and Packaging**

Individual Patches will be packaged in plain plastic wrapping without any markings indicating the dose of the patch contained therein. Labels will be applied to the plastic wrapping of each patch indicating both the study day and dose of the patch (e.g. ‘Day 5: 14 mg’) which will either be accurate or inaccurate depending on experimental group. Labels will also contain a small, 7-digit code number which allows experimenters, but not participants, to identify what type of patch it is (e.g. 14-mg or 14-mg matched placebo). Code numbers will be stored on a hard-drive in the chief investigator’s room at the Smoking Research Unit. Patches for days 1, 8, 15, and 22 will be applied by researchers, with participants given plain cardboard boxes containing the 12 patches for the following six days laid out in order of application.

**6.1.5 Storage**

Patches will be stored at room temperature (20 – 25°C) in sealed boxes inside a dry, unlit storage room in the Smoking Research Unit of the Brain and Mind Research Institute, 100 Mallett St, Camperdown, NSW 2050.

**6.2 PLACEBO PATCHES**

Two types of placebo patches will be required for the study: a 0-mg placebo patch which is physically identical to the 14-mg patch, and a 0-mg placebo which is physically identical to the 7-mg patch. This will allow surreptitious titration of combined nicotine dose in the Unaware group (see Appendix I).

**6.3 DOSING REGIME**

Dosing regime will involve the application of two nicotine patches to dry, clean and hairless skin on the hip, upper arm, or chest every 24 h. Active patches will contain 14 and 7 mg of nicotine, delivered to the participant’s bloodstream through the epidermis.

Participants will be titrated from a starting dose of 21 mg (delivered via a 14- and a 7-mg patch each day) to 0 mg over 28 days, with titrations occurring on average every 7 days (see Appendix I). Participants will attend the clinic once every 7 days where they will have two patches applied by experimenters and will be given the 12 patches to self-apply for the six days before the following visit.

**6.4 RATIONALE FOR STARTING DOSE**

It is a requirement of the study that participants in the Unaware group not be able to tell when their dose is being reduced; however since different dose patches are of different size there is no way to achieve surreptitious dose reductions using single daily patches. Therefore participants will be required to wear two patches per day, with different combinations of patches over the 28-day study period.

Participants will be accepted into the study if they smoke 5 or more cigarettes per day, however they may smoke many more than this. To control for this large range of levels of daily use among participants, a combined starting dose of 21 mg will be administered for the first 7 days of the trial.

**6.5 SUPPORT REQUESTED FROM GSK**

Requested from GSKCH will be 2240 each of 14-mg and 7-mg Nicorette® daily 16-h transdermal nicotine patches and 2240 each of 14-mg matched placebo and 7-mg matched placebo patches, comprising 8960 patches in total (see Table 1).

**Table 1. Breakdown of Nicotine Patches Required in Proposed Expectancy Study**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| *Week* | *Each Participant Requires* | *Total*  *14-mg* | *Total*  *7-mg* | *Total 14-mg placebo* | *Total 7-mg placebo* |
| Week 1 | 7 x 14-mg + 7 x 7-mg | 1120 | 1120 |  |  |
| Week 2 | 7 x 14mg + 7 x 7-mg placebo | 1120 |  |  | 1120 |
| Week 3 | 7 x 14-mg placebo + 7 x 7-mg |  | 1120 | 1120 |  |
| Week 4 | 7 x 14-mg placebo + 7 x 7-mg placebo |  |  | 1120 | 1120 |
| *Total for 28 days* |  | 2240 | 2240 | 2240 | 2240 |

*Note: Total Number per week is based on 160 participants (minimum required to achieve sufficient statistical power to detect a small sized effect after accounting for 15% participant attrition rate).*

**6.6 DOSE CHANGES**

In the event of severe adverse effects caused by the patches themselves, participants will be required to discontinue the treatment.

**6.7 COMPLIANCE**

Compliance will be monitored by researchers during each weekly visit to the Smoking Research Unit via a series of interview questions on several compliance criteria including: abstinence from smoking; daily and correct application of patches; use of psychoactive drugs etc. (see Appendix A.8 for complete questionnaire).

**6.8 OVERDOSE**

In the event of an overdose, a biphasic pattern of symptoms can occur. Initial symptoms are caused by stimulatory effects and can include nausea and vomiting, excessive salivation, abdominal pain, pallor sweating, hypertension, tachycardia, ataxia, tremor, headache, dizziness, muscle fasciculations, and seizures. After the initial stimulatory phase, a later period of depressor effects can occur and may include symptoms of hypotension and bradycardia, central nervous system depression, coma, muscular weakness and/or paralysis, difficulty breathing and/or respiratory failure.

Accidental nicotine overdose involving smoking or nicotine replacement therapies is extremely rare, with most reported cases occurring through the deliberate misuse of and overexposure to one or multiple nicotine sources (i.e. patches, gum, cigarettes) as a form of suicide attempt (Woolf, Burkhart, Caraccio, & Litovitz, 1996). Symptoms of unintentional overdose/poisoning have however been reported in children who misuse nicotine patches (Woolf, Burkhart, Caraccio, & Litovitz, 1997), therefore participants will be warned in person and in the instruction pack to keep nicotine patches out of reach of children (see Appendix G.3 and G.5).

**6.9 PRIOR AND CONCOMITANT MEDICATIONS**

No clinically relevant interactions between nicotine replacement therapy and other drugs have yet been established. Nicotine may however possibly enhance the haemodynamic effects of adenosine i.e. increase in blood pressure and heart rate and also increase pain response (angina-pectoris type chest pain) provoked by adenosine administration. Therefore participants will be told not to take any medication containing either adenosine monophosphate or adenosine triphosphate which while taking part in the trial (see Appendix A.2 for list).

**7. STUDY ASSESSMENTS**

All study assessments are contained in Appendix A

**7.1 PRELIMINARY SCREENING QUESTIONNAIRE**

Participants will be asked for basic demographic data such as age and gender and for number of cigarettes smoked per day.

**7.2 SCREENING AND BASELINE SESSION**

During screening procedures participants will undergo a screening questionnaire, administered by researchers, to determine if they meet eligibility criteria. They will also complete two questionnaires to determine their levels of smoking dependence: the 6-item *Fagerström Test for Cigarette Dependence* (FTCD; Fagerström, 2012) and a demographic and smoking history questionnaire developed by Hendricks and Leventhal (2013) to measure pre-existing differences in smoking behaviour such as number of cigarettes smoked each day, age of smoking onset etc. Carbon Monoxide (CO) meters will be used to verify both extent of dependence (i.e. level of daily use prior to testing). A CO reading of <10 ppm indicates less-than-regular smoking (Benowitz et al. 2002) and will be grounds for exclusion. Pre-existing expectancies surrounding abstinence, withdrawal and ease of quitting will be measured using two scales: a 13-item questionnaire comprised of the *Withdrawal* and *Optimistic Outcomes* subscales of the *Smoking Abstinence Questionnaire* (SAQ; Hendricks et al. 2011) and the *Thoughts About Abstinence* Scale (TAA; Hall, Havassy, & Wasserman, 1990), a 4-item a 4-item questionnaire that will be used to assess motivation to quit, abstinence self-efficacy, perceived difficulty of quitting, and abstinence goals.

Participants will also complete, in the presence of the experimenter, an 8-item online questionnaire. The first 7 items of this questionnaire will be the Mood and Physical Symptoms Scale (MPSS; West & Hajek, 2004), a scale measuring the most common nicotine withdrawal symptoms. The first five items of the MPSS will require participants to indicate, using a 5-item response scale (1–Not at all; to 5–Extremely), to what extent they felt the following symptoms during the past 24 h: Depressed, Irritable, Restless, Hungry, Poor Concentration. The second two items of the MPSS relate to the urge to smoke. The first asks participants to indicate on a 6-item response scale (5–all the time; to 0–Not at all) how much of the time in the past 24 h they have felt the urge to smoke. The second asks participants to indicate on a 6-item response scale (5–Extremely strong; to 0–No urges) how strong the urges referred to in the first item were in the last 24 h. The MAPSS was selected because it possesses sound psychometric properties but is brief enough to be administered regularly. The final item of the daily questionnaire administered to participants will ask them to indicate how many cigarettes, if any, they smoked in the past 24 h. Participants will complete one of these 8-item Withdrawal and Abstinence Questionnaires every single day of the 29-day study, including at the debrief session on day 29.

**7.3 MID-STUDY MEASURES**

Participants will be required to attend the Smoking Research Unit every 7 days for a face-to-face session with researchers. Here they will have their CO level read to confirm abstinence status (≥ 10 ppm indicates recent smoking) and will be interviewed by the researcher enquiring as to their compliance with the guidelines of the study (e.g. if they used illicit or psychoactive drugs, if they smoked, or if they did not apply the patches correctly every day; see Appendix A.8 for full compliance questionnaire).

**7.4 DEBRIEF SESSION**

Participants will have their CO level read, will complete a final Withdrawal and Abstinence Questionnaire and a final Study Compliance Questionnaire. In addition they will complete a probing questionnaire asking them to indicate if, they could detect or suspected any deception in the information provided by to them by researchers (see Appendix D).

**7.5 FOLLOW-UP**

At 1 week, 1 month, and 3 months participants will be contacted by email or phone to enquire if they have relapsed to smoking and, if so, when.

**8. DATA COLLECTION**

Data collection will occur daily (in the case of the online/text message withdrawal and abstinence questionnaire) and weekly (in the case of CO meter readings and questionnaires concerning other drug use). Data will also be collected at 1 week, 1 month and 3 months after the debrief session. Electronic data will be stored on a password-protected computer accessible only to Professor Renee Bittoun, Dr Ben Colagiuri and Mr Llew Mills. Hard-copy data (e.g. weekly ‘other drug use’ questionnaires) will be stored in a locked filing cabinet in Room 310, Griffith Taylor Building (A19), Sydney University, NSW. 2006 for a period of 7 years. After this time the data will be shredded and securely disposed of.

**9. STATISTICS AND DATA ANALYSIS**

**9.1 SAMPLE SIZE CALCUALTION**

Since the study proposed uses a novel procedure, a small effect size of *d*=0.3 was used as a benchmark for determining sample size. Power analysis was conducted using G\*Power version 3.1, which determined that a minimum sample size of *N*=134 (*n*=77) is required to detect an effect of this size. Accounting for a normal attrition rate of 15%, this means that 160 participants are required to achieve sufficient power.

**9.2 PROPOSED ANALYSES**

All primary outcomes are quantitative. In order to determine whether awareness of dose reductions has an effect on reported withdrawal symptoms, cigarettes smoked, and time-to-relapse over the course of the study, a two-way mixed-measures ANOVA will be performed on the data, with Information as the between-subjects factor and Time as the within-subjects factor.

The dependent variable withdrawal symptoms will be calculated as a weekly average of daily scores on the 8-item online withdrawal and abstinence questionnaire. Each weekly period will thus represent a dose period (i.e. 7 days on a combined dose of 21 mg, 7 days on 14 mg, 7 days of 7 mg, 7 days on 0 mg). Similarly, the dependent variable abstinence will be calculated by totalling number of cigarettes smoked for each dose period. Weekly CO meter readings will also be used as a dependent measure of abstinence. The final dependent measure will be Time to Relapse.

Classification variables Duration of Addiction, Number of Cigarettes Smoked Per Day, and Expectations of Withdrawals will be included in a simultaneous multiple linear regression to determine whether these factors a) predict the dependent variables or b) mediate the effect of group allocation on the dependent variables. To determine whether participants’ beliefs about their true dose reduction schedule, rather than treatment group per se, predicts any of the outcome variables, a one-way ANOVA will also be performed on each outcome variable, treating the binary response options in Question 4 (i.e. thought ‘Dose remained the same across the 28 days’ vs thought ‘Dose was reduced over the 28 days’) of the Probing Questionnaire administered on participants’ final visit to the Smoking Research Unit (see Appendix A.9) as two-levels of an IV Belief. Results will be considered significant when *p*<.05.

**10. ADVERSE EVENTS**

The investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects involved in administration of nicotine patches can be found in the instruction pack (see Appendix G.5), which will be given to participants before they leave the baseline session..

Participants should be instructed to contact the investigator at any time after consenting to join the study if any symptoms develop. All reported adverse events (AEs) that occur after joining the trial must be recorded in detail in the case report form (CRF). In the case of an AE, the investigator should initiate the appropriate treatment according to their medical judgement. Participants with AEs present at the last visit must be followed up until resolution of the event.

**10.1 DEFINITIONS**

An **adverse event** (AE) is any untoward medical event affecting a clinical trial participant. An AE can be any unfavourable and unintended sign (including abnormal laboratory findings), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Each additional AE will be considered for severity, causality or expectedness and may be reclassified as a serious event or reaction based on prevailing circumstances.

An **adverse reaction** (AR) is where it is suspected that an AE has been caused by a reaction to a trial drug.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR), or **suspected unexpected serious adverse reaction** (SUSAR) is any AE, AR, or UAR that at any dose:

* results in death
* is life threatening (i.e. the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
* requires hospitalisation or prolongation of existing hospitalisation
* results in persistent or significant disability or incapacity
* is a congenital anomaly or birth defect.

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE. Complications occurring during such hospitalisations will be AEs.

**10.2 DETECTING AEs AND SAEs**

All AEs and SAEs must be recorded from the time a participant consents to join the study until the last study visit.

The investigator and designated study personnel will monitor each participant for adverse events during the study. All adverse events reported between consent and final follow-up will be recorded in a case case report form. The investigator or designee will ask the participant non-leading questions in an effort to detect adverse events eg:

“**How are you feeling?”**

OR

**“Since you were last asked have you felt unwell or different from usual?”**

**In addition subjects be encouraged to spontaneously report any unusual feelings or sensations**

Participants should also be asked if theyhave been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event should be recorded.

**10.3 RECORDING AEs AND SAEs**

Depending on severity, when an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The investigator should then record all relevant information in the case report form and on the SAE form

Information to be collected includes dose, type of event, onset date, investigator assessment of severity and causality, date of resolution as well as treatment required investigations needed, and outcome.

**10.4 EVALUATION OF AEs AND SAEs**

Seriousness, causality, severity, and expectedness should be evaluated as though the participant is taking an active drug. Cases that are considered serious, possibly, probably or definitely related to drug and unexpected (i.e. SUSARs) are likely to be unblinded.

**10.4.1 Assessment of Seriousness**

The investigator should make an assessment of seriousness as defined in Section 10.1.

**10.4.2 Assessment of Causality**

The investigator must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

**Unrelated:** where an event is not considered to be related to the study drug.

**Possibly:** although a relationship to the study drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

**Probably:** the temporal relationship and absence of a more likely explanation suggest the event could be related to the study drug.

**Definitely:** the known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that study drug is the most likely cause.

All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably, definitely) to the study drug will be considered as ARs/SARs. All AEs/SAEs judged as being related (e.g. possibly, probably, definitely) to an interaction between the study drug and another drug will also be considered to be ARs/SARs.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered. The blind should not be broken for the purpose of making this assessment.

**10.4.3 Assessment of Severity**

The investigator should make an assessment of severity for each AE/SAE and record this on the CRF according to one of the following categories:

**Mild:** an event that is easily tolerated by participant, causing minimal discomfort and not interfering with every day activities.

**Moderate:** an event that is sufficiently discomforting to interfere with normal everyday activities.

**Severe:** an event that is sufficiently discomforting to interfere with normal everyday activities.

Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

**10.4.4 Assessment of Expectedness**

If an event is judged to be an AR/SAR, the evaluation of expectedness should be made based on knowledge of the reaction and the relevant product information documented in the investigator’s brochure.

**10.5 REPORTING OF SAEs/SARs/SUSARs**

Once the investigator becomes aware that an SAE has occurred in a study participant, they must report the information to the Pharmacovigilance Sponsor within 24 hours of becoming aware of the event. The SAE form must be completed as thoroughly as possible with all the available details of the event, signed by the investigator or designee. If all the required information is not available at the time of reporting, the investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

The SAE report must provide an assessment of causality and expectedness at the time of the initial report to the Pharmacovigilance Sponsor according to Sections 10.4.2, Assessment of Causality and 10.4.4, Assessment of Expectedness.

**10.6 FOLLOW-UP PROCEDURES**

After initially recording an AE or recording and reporting an SAE, the investigator is required to follow each participant until resolution. Follow up information on an SAE should be reported to the Pharmacovigilance Sponsor.

Unless otherwise stated in the protocol, AEs and SAEs should be followed up until resolution or death of the trial subject.

**11. PREGNANCY**

Pregnancy is not considered an AE or SAE however the investigator must collect pregnancy information for female trial subjects or female partners of male trial subjects who become pregnant while participating in a study. The investigator should record the information on a Pregnancy Notification Form and submit this to the Pharmacovigilance Sponsor within 14 days of being made aware of the pregnancy.

Any pregnancy that occurs in a trial subject or trial subject’s partner during a trial should be followed to outcome. In some circumstances, it may be necessary to monitor the development of the newborn for an appropriate period post delivery.

**12. MONITORING AND QUALITY ASSURANCE**

**12.1 PROJECT MANAGEMENT GROUP**

The trial will be coordinated by a project management group, consisting of the chief and other investigators.

**12.2 RISK ASESSMENT**

**12.2.1 Potential Risks**

Participants will have two nicotine patches per day applied, either by themselves or by researchers. The Nicotine patches that will be used in the trial have been used clinically, have been commercially available over the counter for many years, and have been proven to be safe. However minor side-effects such as anxiety, constipation, diarrhea, dizziness, fatigue, headache, insomnia, irritability, mild itching/burning/redness/tingling at site of application, or upset stomach may occur during the treatment. More serious side-effects such as chest pain, irregular heart-beat or heart palpitations, leg pain, severe stomach upset, skin rash or swollen skin, symptoms of a severe allergic reaction (eg. hives, difficulty breathing or swelling of the face and throat) can occur in certain rare circumstances. The more severe adverse events relate to nicotine poisoning (which cannot occur unless patches are used in conjunction with ingestion of extremely high levels of other sources of nicotine) include abdominal or stomach pain, cold sweat, confusion, convulsions (seizures), disturbed hearing and vision, drooling, extreme exhaustion, pale skin, rapid heart beat, and tremors. Accidental nicotine overdose/poisoning in adults using transdermal nicotine patches is extremely rare, with no cases reported in the literature (Woolf et al. 1996). Children however have shown symptoms of overdose following application or ingestion of nicotine patches (Woolf et al. 1997). These unintentional exposures required treatment in hospital, however this treatment involved only skin decontamination and supportive care and resulted in the rapid abatement of symptoms.

**12.2.2 Minimising Risk**

While risks of the occurrence of adverse events have been minimised to some extent by excluding participants with have no prior history of cardiovascular disease, hypertension, diabetes, renal impairment, chronic dermatological disorders, moderate to severe allergies, or diagnosed mental disorders, the possibility still remains that adverse events may occur. This risk can be minimised by closely monitoring the participant during the weekly face-to-face interviews. Participants will also be encouraged to contact the researcher immediately should an adverse event occur. All chief and other investigators will be contactable at any time during the trial (details provided on the Participant Information Sheet). If the participant experiences adverse physical or psychological reaction to the patches they will be instructed to remove the patches immediately, withdraw from the study, and all appropriate measures as indicated by medical practitioners with the participant’s consent will be taken.

In order to avoid the possibility of children accidentally being exposed to participants’ nicotine patches, all participants will be warned verbally by experimenters, and in writing in the instruction pack (see section G.3 and G.5), to keep nicotine patches are kept out of reach of children.

**13. GOOD CLINICAL PRACTICE MODULE**

**13.1 ETHICAL CONDUCT OF THE STUDY**

This study will be carried out according to the Declaration of Helsinki, the NHMRC National Statement on Ethical Conduct in Research Involving Humans (1999) and the Notes for Guidance on Good Clinical Practice as adopted by the Australian Therapeutic Goods Administration (2000) (CPMP/ICH?135/95) and the ICH GCP Guidelines [1].

The protocol and related documents will be submitted for review by the Human Research Ethics Committee (HREC) and written approval received before the study commences.

**13.2 INVESTIGATOR RESPONSIBILITIES**

The investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of GCP, the following areas listed in this section are also the responsibility of the investigator. All face-to-face sessions and other responsibilities will be conducted by the chief and other investigators.

**13.2.1 Informed Consent**

O’Neil and Miller (2009) suggest that ethical review boards can approve alterations to informed consent requirements if four criteria are met. We will address each in turn with regards to the proposed study.

1. **The research involves no more than minimal risk to the subjects:**

* This study will be assisting moderate to heavy smokers discontinue a physically harmful practice using a commercially-available nicotine replacement therapy with minimal side-effects if used as directed. The study will do this using a standard method of quitting: tapered dose-reduction. Thus the research involves no more than minimal risk to participants.
* The only distress that could potentially occur in this study due to the study itself (i.e. that would not occur if participants undertook to quit smoking using a tapered nicotine patch dose reduction regimen of their own volition) is that participants in the Unaware group could experience more significant withdrawal symptoms than they expect. However since participants will likely be experiencing withdrawals, especially cravings, of some kind anyway, due to their discontinuation of smoking, and because they will be tapered off their nicotine patches slowly, the likelihood of the severity of their withdrawals serving as a interoceptive cue disconfirming the expectancies generated by their treatment condition will most likely be quite low.

1. **The alteration will not adversely affect the rights or welfare of participants.**

* The principal right or issue that will be affected by the proposed study is the right to not be experimented on without valid, that is, informed consent. Some studies however require the absence of a valid consent process because that consent process gives information that invalidates the purpose of the research.
* If the infringement of the right to informed consent is a necessary part of the study design, then the criteria by which a study may be granted an alteration rests on whether the anticipated objectives of the study provide sufficiently good reason to infringe participants rights to be informed about the true purpose of the study. These criteria are:

1. *The value of the study:* The study aims to quantify the role expectancies of withdrawals play in overall withdrawal symptoms experienced during a tapered dose reduction regimen. Findings from this study will provide an evidentiary basis for the design of future interventions which may help individuals addicted to smoking to discontinue a physically and financially detrimental practice.
2. *The degree of the infringement:*The only infringement in the study will be that the Unaware group will have their dose reduced when they believe it is remaining stable. We argue that this represents a minor infringement of their right to be informed since in the Participant Consent form they will be informed that the study will require the daily application of nicotine patches over 28 days to aid in smoking cessation, all of which will occur.
3. *Alternatives to Infringement:*This trial involves the removing of negative expectancies in order to reduce withdrawal symptoms. As such telling participants the purpose, procedures and likely consequences of the study is not possible without influencing the outcome variables of interest: withdrawal and relapse. Therefore deception is a necessary component of this study, as it is with a great deal of placebo research. Kirsch and Weixel (1988) demonstrated that alerting participants to the possibility of receiving a placebo prior to random allocation to either treatment or placebo condition – as occurs in double-blind placebo trials ­– delivered results that were either reduced or in the opposite direction of those obtained when participants were not told that they may receive a placebo (deceptive administration). The authors argued that double-blind administration actually leads to an underestimation of the effect that beliefs and expectancies have on treatment outcomes. Since the express purpose of the proposed study is to quantify the role these expectancies play in withdrawal symptoms, we would argue that deceptive administration of a tapered dose reduction regimen to the Unaware group is necessary to the scientific validity of the study.
4. **The research could not practicably carried out without the deception.**

See Item 2 c) *Alternatives to Infringement* for reasons why the research cannot be carried out without the deception.

1. **Whenever appropriate, the subjects will be provided with additional pertinent information after participation.**

Upon completion of the study participants will be fully debriefed as to the true purpose of the study, the true procedures undertaken, and why the deception was necessary for the validity of the study. Participants will be permitted to withdraw their data from the study following the debriefing session should they wish.

**13.3.3 Emergency Contact with Investigators**

All participants will be provided with a Participant Emergency Contact Card with contact details concerning whom to contact in the case of an emergency (See Appendix A).

**13.3.4 Notification of Primary Care Physician**

With the consent of the volunteer, it is the investigator’s responsibility to notify the primary care physician of the participant’s participation in the study, provided that such a physician can be identified for the participant and his/her notification is relevant for the particular circumstances of the of the trial. Where relevant a letter will be sent to the physician stating the nature of the study, treatments, expected benefits or adverse events and concomitant drugs to be avoided. A copy shall be retained by the study site for verification by the Study Monitor.

**13.3.5 Investigator Indemnification**

The study is being conducted subject to the ‘Guideline for Compensation for Injury Resulting from Participation in an investigator-sponsored clinical trial’ published by Medicines Australia. The University of Sydney will reimburse participants for costs of medical care that occur as a result of complications directly related to participation in this study.

**13.3.6 Study Site Staff**

The investigator must be familiar with the investigational product, protocol and the study requirements. The investigator will be the study’s sole administrator, however in the event that investigator is unable to attend any face-to-face sessions, it is the investigator’s responsibility to ensure that all staff assisting with the study are adequately informed about the investigational product, protocol and their trial-related duties.

**13.3.7 Data Recording**

The investigator is responsible for the quality of the data recorded in the case report form.

**13.3.8 Confidentiality**

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by regulatory authorities or the HREC. The investigator and any study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study.

**13.3.9 Data Protection**

All investigators and study site staff involved with this study must comply with the requirements of the appropriate Data Protection or Privacy Act with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles. Access to collated participant data will be restricted to those clinicians treating participants.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

**14. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS**

**14.1 AUTHORSHIP POLICY**

Ownership of the data arising from this study resides with the study team, that is the Chief and Other investigators. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

**14.2 PUBLICATION**

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish, orally or in writing, the results of the study.

Summaries of results will also be made available to investigators for dissemination within their clinics (where appropriate and according to their discretion).

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**APPENDIX A – QUESTIONNAIRES**

**A.1 Online Smoking and Demographics Screening Questionnaire**

1. **Demographic Information**

**Please indicate your gender**

* Male
* Female
* Other (please indicate) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Please enter your age (in years)

**Please indicate your employment status**

* Full time
* Part time
* Volunteer
* Unemployed
* Student
* Retired
* Other (please indicate) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Please indicate your highest level of education**

* Primary
* Secondary
* College / University
* Other (please indicate) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Please indicate your marital status**

* Single
* In a relationship
* Cohabitating
* Married
* Divorced
* Widowed
* Other (please indicate) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Please indicate your predominant ethnicity** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**2. Smoking**

**Do you smoke cigarettes every day?**

* Yes
* No

**If you indicated ‘Yes’ above, please indicate how many cigarettes you would smoke on an average weekday.**

* 1 - 2
* 3 - 5
* 5 – 10
* 10 - 20
* If more than 20 per day, please indicate how many

1. **Internet and Phone Access**

This study requires its participants to be able to complete surveys over the internet.

**Do you have daily access to the internet?**

* Yes
* No

**If you answered yes above, please indicate how you access the internet (you can tick both)**

* Smartphone (i.e. iPhone or android)
* Computer (i.e. desktop or laptop)

**If you answered ‘Computer’ only above, do you have the internet at home or do you access it somewhere else?**

* At Home
* Somewhere else (e.g. at university, a friend’s place, an internet café etc.)

**End of Survey**

Thankyou for completing this questionnaire. Please indicate your email address in the box below and we will send you an information sheet.

**A.2 Screening Interview Questions for Study Eligibility (to be asked of participants in person at Baseline Session by researchers).**

**Medical Questionnaire**

Date:

Name:

Sex:

Date of Birth:

**Present Medical Problems**

Please list any known medical problems that you have at present

Medical Problems Date of Onset Comments

**Current Medication**

Please list all medications that you are currently taking

(including insulin, oral contraceptives, over-the-counter medications, vitamins, supplements, herbal preparations etc.)

Medication Taken For Dosage Doses per day Date Started

**Significant Past Illnesses/Surgeries**

Please list significant illnesses or surgeries that have had as a child or adult.

Illness/Surgery Year(s) Comments

**Drug Reactions/Allergies**

Please list all known reactions/allergies to any medications.

Illness/Surgery Type of reaction/allergy Year(s)

**Study Inclusion checklist (desired answer for inclusion = Yes)**  Yes No

* Over 18 yrs old
* Daily internet access

**Study Inclusion checklist** (continued) Yes No

* CO reading > 10 ppm
* Not currently planning to be pregnant/breastfeeding
* No current/history of chronic dermatological disorders?
* No current/history of moderate to severe allergies?
* No current/history of heart-attack or abnormal arrhythmias
* No current/history of cardiovascular disease,
* No current/history of hypertension,
* No current/history of diabetes
* No current/history of renal impairment

(i.e. abnormal heart rhythm)

* No severe or worsening angina
* Have not recently suffered a stroke
* Not taking medication containing adenosine i.e. for treatment

of acute kidney failure, high blood pressure/pulmonary

hypertension, cystic fibrosis, lung cancer, irregular heartbeat

* Not on nicotine replacement therapy (eg. patches, gum ,

inhalant) of any kind for the 3 months prior to commencement

of the study?

* Not a regular/dependent user of psychoactive drugs, legal or

illegal, other than caffeine or alcohol

* Not currently suffering from a diagnosed mental disorder

(eg. depression, social anxiety, ADHD)?

* Has not received any therapy or drug used to aid in the

cessation of smoking (eg. nicotine gum, Chantix®,

hypnotherapy) for thirty days prior to being admitted to

the study.

* Not participating in another clinical trial for an experimental

drug for the thirty days prior to the study.

* Not currently taking any of the following medications:
  + Acetaminophen,
  + Adenosine
  + benzodiazepines (e.g., oxazepam, valium)
  + furosemide,
  + imipramine
  + insulin
  + labetalol
  + peginterferon alfa-2b
  + phenylephrine
  + prazosin
  + propranololtheophylline

**Suitability**

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| Are you able to attend 4 more appointments over the 29-day trial? |  |  |
| Are you able and willing to wear two nicotine patches each day as directed? |  |  |
| Are you able and willing to complete a 1-2 min online survey each day? |  |  |
| Are you willing to be contacted for a 1-min follow-up phone interview at 1 week, 1 and 3 months from completion of the study? |  |  |
| Can you speak and read English? |  |  |

**Participant details**

Mobile Phone                                    Address

Home Phone

Work Phone

Email

Preferred Method of Communication

|  |  |
| --- | --- |
| Participant Information Statement Received | ☐ |
| Participant Consent Form Received | ☐ |
| Instruction Pack Received | ☐ |
| Patches for Next Week Received | ☐ |

**A.3 Expectancy of Withdrawal Scale – taken from the Smoking Abstinence Questionnaire (SAQ; Hendricks & Leventhal 2012)**

We would like to learn about what you would expect to happen if you quit smoking. Below are a number of sentences. Each sentence is about a consequence that might happen if you quit smoking. Please rate how LIKELY or UNLIKELY you believe each consequence would be for you if you quit smoking.

For example:

If a consequence seems not at all likely to you, you would circle 0. If a consequence seems extremely like to you, you would circle 6. If it seems neither likely nor unlikely, you would circle 3. Please refer to the scale below to guide you further:

0 1 2 3 4 5 6

Not likely at all Very unlikely Somewhat unlikely Neither likely nor unlikely Somewhat likely Very likely Extremely likely

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| *If I quit smoking……* | *Not likely*  *at all* |  |  |  |  |  | *Extremely likely* |
| 1. I would have few urges or cravings to smoke. (oo) | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 2. The sight of a cigarette would tempt me to smoke. (w) | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 3. I would feel short-tempered or cranky (w) | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 4. My weight would not change. (oo) | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 5. My mood would not be affected. (oo) | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 6. The demands of everyday life would seem like more of a struggle. (w) | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 7. I would really crave a cigarette. (w) | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 8. It would be no problem to find an alternative to smoking that helps reduce stress.(oo) | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 9. My ability to deal with stress would not be affected.(oo) | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 10. All I would think about is having a cigarette. (w) | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 11. I would feel anxious, nervous or worried.(w) | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 12. Withdrawal would not be much of a problem for me.(oo) | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 13. Seeing someone else smoke would make me crave a cigarette. (w) | 0 | 1 | 2 | 3 | 4 | 5 | 6 |

*Note: Items taken from the Smoking Abstinence Questionnaire (Hendricks et al. 2011). (oo) indicates items taken from the optimistic outcomes scale, (w) indicates items take from the withdrawal scale.*

**A.4 Fagerström Test for Cigarette Dependence (FTCD; Fagerström, 2012)**

**PLEASE CHECK THE APPROPRIATE ANSWER.**

1. How soon after you wake up do you smoke your first cigarette?

* After 60 minutes
* 31 – 60 minutes
* 6 – 30 minutes
* Within 5 minutes

1. Do you find it difficult to refrain from smoking in places where it is prohibited, such as in church, at the library, or in the movies?

* No
* Yes

1. Which cigarette would you hate most to give up?

* First cigarette in the morning
* Cigarette during or after meals
* Cigarette during or after stressful situations
* None of the above

1. How many cigarettes a day do you smoke?\*

* Less than 10
* 11 – 20
* 21 – 30
* 31 or more

1. Do you smoke more frequently during the first two hours of the day than during the rest of the day?

* No
* Yes

1. Do you smoke when you are so ill that you are in bed most of the day?

* No
* Yes

**A.5 Tobacco History Questionnaire (Hendricks & Leventhal, 2012)**

|  |  |
| --- | --- |
| On average, how many cigarettes do you smoke per day? |  |
| How old were you when you smoked your first cigarette? |  |
| How old were you when you first became a regular cigarette user? |  |
| How old were you when your first became a daily cigarette user? |  |
| Do you typically smoke menthol cigarettes? |  |
| What brand(s) of cigarette do you typically smoke? |  |
| How is cigarette smoking handled in your home? (Check one) |  |
| Total Ban (no one is allowed to smoke cigarettes in my home) |  |
| Some Restrictions (only special guests are allowed to smoke cigarettes in my home or people are allowed to smoke cigarettes only in certain areas in my home) |  |
| No Restrictions (people are allowed to smoke cigarettes anywhere in my home) |  |
| Have you ever tried to quit smoking? If so… |  |
| How many times have you quit smoking for at least 24 hours? |  |
| How many times have you quit smoking for at least 7 days? |  |
| What is the longest time that you have been able to quit smoking during any one of your quit attempts? |  |

**A.6 Thoughts About Abstinence Scale (Hall et al. 1990)**

1. First, I’d like to know how you feel about stopping smoking cigarettes at this time. On a scale from 1 to 10, with 1 representing no desire to quit and 10 representing full desire to quit, give yourself a rating. Circle the number between 1 and 10 that best describes your own desire to stop smoking cigarettes at this time. Remember, the higher the number, the greater your desire.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| No desire to quit |  |  |  |  |  |  |  |  | Full desire to quit |

1. Now, I’d like to know how successful you expect to be quitting smoking cigarettes at this time. Be realistic about this, based on your past experiences and your present strength of motivation. On a scale from 1 to 10, with 1 representing the lowest expectation of success and 10 representing the highest expectation of success, give yourself a rating of your own expectation of success in quitting smoking cigarettes. Remember, the higher the number, the greater the expectation of success.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| Lowest expectation of success | |  |  |  |  |  |  | Highest expectation of success | |

1. Now, I’d like to know how difficult you think it will be for you to keep from smoking cigarettes after having quit. On a scale from 1 to 10, with 1 representing the lowest amount of difficulty and 10 representing the greatest amount of difficulty, give yourself a rating of how difficult you think it will be for you to quit and remain abstinent. Remember, the higher the number, the more difficult you think it will be for you to quit.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| Lowest  amount of difficulty | |  |  |  |  |  |  | Highest amount of difficulty | |

1. Lastly, I want to know the GOAL you have chosen for yourself about smoking cigarettes at this time.

Please read the goals listed on this page and circle the one goal that best represents your own goal at this time, and fill in blanks as indicated.

1 – I really don’t have a clear goal in mind.

2 – I want to use cigarettes in a controlled manner – to be in control of how often I smoke and how much I smoke. I would like to limit that to no more than \_\_\_\_\_\_\_\_\_\_ (amount) per \_\_\_\_\_\_\_\_\_\_ (time).

3 – I want to be totally abstinent from all cigarette use for a period of time, after which I will make a new decision about whether or not I will smoke cigarettes again. For me, the time period I want to be abstinent for is: \_\_\_\_\_\_\_\_\_\_ (time).

4 – I don’t want smoking cigarettes to be a habit for me anymore, but I would like to be able to occasionally smoke cigarettes when I really have an urge.

5 – I want to quit smoking cigarettes once and for all, even though I realize I may slip up and smoke cigarettes once and a while.

6 – I want to quit smoking cigarettes once and for all, to be totally abstinent, and never smoke cigarettes ever again for the rest of my life.

7 – None of the above applies exactly to me. My own goal is:

**A.7 Withdrawal and Abstinence Questionnaire (to be completed online daily by participants).**

**Part 1: Mood and Physical Symptoms Scale (MPSS; West and Hajek, 2004)**

Please show for each of the items how you have been feeling over the past 24 hours

(circle one number for each item)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Not at all | Slightly | Somewhat | Very | Extremely |
| Depressed | 1 | 2 | 3 | 4 | 5 |
| Irritable | 1 | 2 | 3 | 4 | 5 |
| Restless | 1 | 2 | 3 | 4 | 5 |
| Hungry | 1 | 2 | 3 | 4 | 5 |
| Poor concentration | 1 | 2 | 3 | 4 | 5 |

How much of the time have you felt the urge to smoke in the past 24 h? (circle one number)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| All  the time | Almost all the time | A lot of the time | Some of the time | A little of the time | Not  at all |
| 5 | 4 | 3 | 2 | 1 | 0 |

How strong have the urges been? (circle one number)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Extremely Strong | Very  Strong | Strong | Moderate | Slight | No  urges |
| 5 | 4 | 3 | 2 | 1 | 0 |

**Part 2: Abstinence Question**

How many cigarettes have you smoked in the past 24 h

* 1
* 2
* 3 - 5
* 5 - 10

If more than 10, please indicate how many

**A.8 Compliance Interview Questions (to be answered in person by participants at weekly face-to-face sessions).**

The following is a list of questions designed to determine if you have been complying with the conditions of ongoing participation in the study. These conditions were included to protect participants health and wellbeing so please answer truthfully.

**1. Did you smoke any cigarettes or e-cigarettes in the last week? If so, please provide details (how many, which days etc.)**

* Cigarettes
* e-cigarettes

**2. Did you take any form of nicotine replacement therapy in the last 7 days, other than the patches provided to you by the researchers? If so, please provide details (what kind, which brand, how many, which days etc.)**

* nicotine patches
* nicotine gum
* nicotine lozenges
* nicotine mouth spray
* nicotine nasal spray

**3. Did you take any drug aimed at reducing or quitting smoking in the last 7 days, other than the patches provided to you by the researchers? If so, please provide details (what kind, which brand, how many, which days etc.)**

* Bupropion (Zyban®)
* Varenicline (Chantix®)
* Other

**4. Did you take part in any form of therapy or counselling aimed at reducing or quitting smoking in the last 7 days. If so, please provide details (what form, how often, which days etc.)**

* Self-Help (manuals, pamphlets, videos, books, online courses etc.)
* Telephone or call-back counselling (eg. quitline)
* Hypnotherapy
* Cognitive Behavioural Therapy
* Other

**5. In the last 7 days, did you enrol in another clinical trial for an experimental drug and/or consume any of the drug that was the subject of this trial. If yes, please provide details.**

* No
* Yes

**6. In the last 7 days, did you consume any form of psychoactive drug, legal or illegal, other than caffeine or alcohol? If yes please provide details (what type of drug, how much, how often etc.)**

* Anti-depressants
* Benzodiazepam
* Ritalin
* Marijuana
* Amphetamine
* LSD or Ecstasy
* Heroin
* Other

**7. Over the last 7 days, did you apply two patches per day in the correct order (i.e. both a large and a small patch each day) according to the labels on the patches and the dosing table given to you by experimenters, which was contained on the Participant Information Sheet sheet given to you by experimenters at your first visit to the Smoking Research Unit? If you did not, please provide details (which days, why not etc.)**

* Yes
* No

**8. Over the last 7 days, did you have any problems concerning the completion of the daily online questionnaires. If yes, please provide details.**

* Yes
* No

**9. Were there any other problems you may have experienced in the last 7 days which may have caused you to have trouble complying with the conditions for participation in the study as outlined in the ‘Study Requirements’ section of the Participant Information Statement? If yes, please provide details. For example did you begin taking medication which was contraindicated for use alongside nicotine patches.**

* No
* Yes

**8. Since you were last asked have you felt unwell or different from usual?**

* Yes
* No

**A.9 Probing Questionnaire for Awareness of Study Deception (note: to be administered prior to debriefing)**

**Nicotine Study Exit Questionnaire**

**1. Did you think the experimental procedures differed in any way from what you had been told? If yes, tell us how you think they differed.**

* No
* Yes

**2. Tell us what you think the purpose of the study was.**

**3. Do you have any other comments on the testing or procedure?**

**4. Do you think that the combined dose of your nicotine patches remained the same across the 28-day study period, or do you think your dose was reduced?**

* Dose remained the same across the 28 days
* Dose was reduced over the 28 days

**Estimate how likely it was that your dose was reduced**

* Certainly reduced
* Probably reduced
* Possibly reduced
* Do not know
* Possibly stayed the same
* Probably stayed the same
* Certainly stayed the same

|  |
| --- |
| **USY_MB1_RGB_Standard_Logo.tif School of Psychology** |
|  |
| **Dr Ben Colagiuri**  Room 444  Lecturer Brennan MacCallum, A18  The University of Sydney  NSW 2006 AUSTRALIA  Telephone: +61 2 9351 4589  Facsimile: +61 2 9351 5223  Email: ben.colagiuri@sydney.edu.au  Web: <http://www.sydney.edu.au/> |

**THE EFFECT OF DIFFERENT NICOTINE-PATCH**

**APPENDIX B – PARTICIPANT INFORMATION STATEMENT**

**DOSING REGIMENS ON WITHDRAWAL SYMPTOMS**

1. **What is the study about?**

You are invited to take part in a study investigating the effects that different ways of coming off nicotine patches have on withdrawal symptoms. The findings from this study will be used to determine which method of coming off nicotine patches leads to the lowest withdrawals and the longest time without going back to smoking cigarettes.

1. **Who is carrying out the study?**

The study is being conducted by Llew Mills from the University of Sydney as part of his PhD research, under the supervision of Dr Ben Colagiuri and Professor Renee Bittoun.

1. **Why is the study being run?**

A nicotine patch is a way of replacing the nicotine you get from cigarettes—which is absorbed through the lungs—with nicotine absorbed through the skin. This is so you can concentrate on dealing with the habitual side of your addiction—i.e. changing your routine to adjust to life without cigarettes—without suffering the physical withdrawals and cravings you would get if you stopped your body’s supply of nicotine altogether.

Two methods have been used in the past to come off nicotine patches:

a) staying on the same dose for a fixed period then just stopping patches altogether

b) gradually reducing the dose of patch over time before stopping altogether.

Each of these methods has been shown to give people addicted to smoking a much better chance of quitting long-term than going ‘cold turkey’, but we don’t know a lot about how the two methods compare to eachother in terms of withdrawals and relapse. We want to test this by assigning you randomly to one of two groups, a Fixed group [which will use method a) above] and a Reduction group [which will use method b)].

**4) What will the study involve?**

If you choose to take part in the study you will be required to wear two nicotine patches per day —a large and a small one—for 28 days. These patches will be provided to you free of charge. The patches will be labelled so you will know which patch to apply and when to apply it (details will be provided in the Instruction Pack you will receive at the end of the session today). We will show you how to apply the patches today, but for the majority of the study we will ask you to apply the patches yourself. We will give you instructions—which we also be included in the instruction pack in case you forget—about how and when to apply the patches to ensure they are as comfortable and unnoticeable as possible.

You will also be required to complete one very short (i.e. less than 60 sec) questionnaire each day, either on your smartphone or your computer, detailing how you have been feeling for the past 24 hours and whether you have smoked. The researcher will show you how to do this before you leave today.

You will be required to come back here to the Smoking Research Unit every 7 days to have a ten minute face-to-face session with the experimenter. This session is so we can check whether you have had any problems during the week so we can give you your patches for the following 7 days. There will also be a final face-to-face session on day 29.

If you decide to take part in the study we will ask you to fill out four short questionnaires today, so we can get an idea of your smoking history and the expectations you have about quitting smoking. This should only take about 30 – 45 minutes. Then we will show you how to apply your first patch, give you your patches for the next 7 days and you can leave.

Because we want to know if the dosing method people use to come off nicotine patches has any long term effects on their ability to remain abstinent (i.e. to ‘stay quit’) we hope you will consent to us contacting you 1 week, 1 month, and 3 months after the study has ended to ask how your quit attempt is going.

*Study Requirements*

There are several requirements we have of you to take part in this study. Please read these **very carefully** as they are vital for the success of the study.

* 1. The most important is that you **don’t smoke**for the duration of the 28 days you are on nicotine patches. We would also ask you not to smoke e-cigarettes.
  2. Secondly we ask that you make sure **you apply *both* patches as instructed every day for the 28 days of the study**. Please look carefully at the labels on the patches each day to make sure you are applying the correct patch on the correct day. This applies to the people assigned to the Fixed group as well, since the labels will let you know how far you are through the study and thus how long you have to go (also because we need to make sure both groups are given exactly the same procedure in every way apart from the strength of their patches). We ask that you hold on to the foil wrappers that the patches come wrapped in and return them to us at each weekly face-to-face session so that the researchers can verify that you have been applying the patches each day.
  3. Because many of the withdrawal symptoms abstinent smokers experience are psychological, we need to make sure that the symptoms you experience are due to you stopping smoking and not because you consumed some other kind of drug. Therefore we also ask that you consume **no psychoactive drugs of any kind during the 28 days of the study.** This includes both legal prescription drugs (such as anti-depressants, valium, xanax, ritalin etc.) and illegal drugs (such as marijuana, ecstasy, acid, speed, cocaine, heroin etc.). However you will be permitted to consume caffeine and alcohol in moderate amounts over the 28 days.
  4. We ask you **not to start** **any other form of treatment to help you stop smoking** over the course of the study. This includes:
     1. any types of nicotine replacement therapy such as nicotine gum, lozenges, inhalant or nasal spray
     2. drugs such as Chantix® or Zyban®
     3. any kind of self-help materials to quit smoking such as pamphlets, books, online tutorials, DVDs etc.
     4. any kind of counselling, such as hypnotherapy, phone counselling, cognitive behavioural therapy etc.
  5. We also ask that you **not enrol in another clinical trial for an experimental drug** during the study.

This study is aiming to help people by improving our knowledge of the best way to assist smokers such as yourself to stay quit for good, so please follow the requirements outlined above and hopefully we can work together to make sure the time and effort you put in in helping us was well spent.

1. **Will the study be dangerous?**

No. Use of Nicotine patches is very widespread and there is little chance of you experiencing adverse effects if the patches are used as intended. However we encourage you to let researchers know at any time, day or night, if you feel unwell or different from usual.

1. **How much time will the study take?**

The study itself will last 29 days, however you will only need to attend the Smoking Research Unit five times over that time. Today’s session will last 60 min. You will then be required to attend each week for 3 weeks for a 10-min face-to-face session. There will also be a final visit on day 29 which will last 20 min. So your total face-to-face time will be about two hours in total.

1. **Can I withdraw from the study?**

Being in this study is completely voluntary – you are not under any obligation to consent – you can withdraw at any time without affecting your relationship with the University of Sydney.

1. **Will anyone else know the results?**

All aspects of the study, including results, will be strictly confidential and only the researchers will have access to information on participants. A report of the study may be submitted for publication, but individual participants will not be identifiable in such a report*.* Other researchers may also be granted access to de-identified data for the purpose of further analysis. This data will not include participant names or any other information that could identify you.

1. **Will the study benefit me?**

You will receive $50 to cover any out-of-pocket expenses to do with your participation.

1. **Can I tell other people about the study?**

You are welcome to discuss the study with other people, such as your family and friends. However we do ask that you try to avoid discussing it with other participants as sometimes this can affect the study’s results.

1. **What if I require further information about the study or my involvement in it?**

When you have read this information, Llew MIlls will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact *him* via email at lmil8126@unisydney.edu.au or via phone on 04212 032 614.

1. **What if I have a complaint or any concerns?**

Any person with concerns or complaints about the conduct of a research study can contact The Manager, Human Ethics Administration, University of Sydney on +61 2 8627 8176 (Telephone); +61 2 8627 8177 (Facsimile) or [ro.humanethics@sydney.edu.au](mailto:ro.humanethics@sydney.edu.au) (Email).

*This information sheet is for you to keep*

|  |  |  |  |
| --- | --- | --- | --- |
| **APPENDIX C – PARTICIPANT CONSENT FORM** | |  |  |
| USY_MB1_RGB_Standard_Logo.tif | ABN 15 211 513 464 | | **School of Psychology** |
|  | **Dr Ben Colagiuri**  **Lecturer** | | Room 444  Brennan McCallum A18  The University of Sydney  NSW 2006 AUSTRALIA  Telephone: +61 2 9352 4589  Facsimile: +61 2 9351 5223  Email: [ben.colagiuri@sydney.edu.au](mailto:ben.colagiuri@sydney.edu.au)  Web: <http://www.sydney.edu.au/> |

**PARTICIPANT CONSENT FORM**

I, ...........................................................................................[PRINT NAME], give consent to my participation in the research project.

TITLE: THE EFFECT OF DIFFERENT NICOTINE-PATCH DOSING REGIMENS ON WITHDRAWAL SYMPTOMS

In giving my consent I acknowledge that:

1. The procedures required for the project and the time involved have been explained to me, including any inconvenience, risk, discomfort or side effect, and their implications and any questions I have about the project have been answered to my satisfaction.
2. I have read the Participant Information Statement and have been given the opportunity to discuss the information and my involvement in the project with the researcher/s.
3. I understand that being in this study is completely voluntary – I am not under any obligation to consent.
4. I understand that my involvement is strictly confidential. I understand that any research data gathered from the results of the study may be published however no information about me will be used in any way that is identifiable.
5. I understand that I can withdraw from the study at any time, without affecting my relationship with the researcher(s) or the University of Sydney now or in the future.
6. I may be contacted by researchers after the study is completed to enquire about my smoking habits.

Signature

Please PRINT name

Date

|  |  |  |  |
| --- | --- | --- | --- |
| **APPENDIX D – DEBRIEF STATEMENT**  USY_MB1_RGB_Standard_Logo.tif | |  |  |
|  | ABN 15 211 513 464 | | **School of Psychology** |
|  | **Dr Ben Colagiuri**  **Lecturer** | | Room 444  Brennan McCallum A18  The University of Sydney  NSW 2006 AUSTRALIA  Telephone: +61 2 9352 4589  Facsimile: +61 2 9351 5223  Email: [ben.colagiuri@sydney.edu.au](mailto:ben.colagiuri@sydney.edu.au)  Web: <http://www.sydney.edu.au/> |

**THE EFFECTS OF EXPECTANCIES ON WITHDRAWAL SYMPTOMS**

**DEBRIEF STATEMENT**

Thankyou for participating in this study. The aim of this study was to examine the cognitive processes involved in negative placebo effects. A placebo effect refers to when a drug or procedure causes effects that aren’t due to the drug or procedure itself. Placebo effects can be positive (e.g. the pain relief a patient feels when they are told a simple sugar pill is morphine) or negative (e.g. the nausea a patient receiving chemotherapy feels when they are given an injection of water in the same room as the chemotherapy drugs were injected with in the past). Placebo effects are mostly caused by the expectation of receiving a particular treatment (i.e. a drug or procedure). These expectations are generated when we receive information that causes us to believe a particular drug or treatment is about to happen. For example studies have shown people who believe they have just consumed alcohol feel and behave drunk even when they have not received any alcohol.

We wondered if the same principle might apply to expectations of feeling withdrawals, specifically whether a group of abstinent smokers who knew their combined dose of nicotine patch was about to be reduced would experience more withdrawal symptoms than a group whose dose was reduced without their knowledge.

In this study, some people were led to believe that their combined dose of nicotine patches stayed the same across the 28 days of the study. In fact all participants had their dose of nicotine reduced gradually across the 28 days. Furthermore for the final 6 days of the study all participants were wearing patches that contained no nicotine at all (i.e. 0-mg placebo patches).

Because research into the effect of expectations on treatment outcomes requires that people believe they are receiving an active treatment, it was necessary for us to keep the true purpose of the study hidden from you until after you had completed all of the required tests. We apologise for the deception and for not revealing the study’s true aims. After reading this you have the right to withdraw your data from the study. Please inform one of the researchers if you wish to do this and be assured that there will be no repercussions if you choose to do this.

If you would like to know more about the study, your performance in any of the tests, or the results of the study please contact Llew Mills on 0421 032 614 or at [lmil8126@uni.sydney.edu.au](mailto:lmil8126@uni.sydney.edu.au) and he will arrange to make these available to you.

Meanwhile, because it is important that other participants do not know precisely what we are looking for before they are tested, we ask for your help by not telling other people that might participate in this study in future.

Once again, thankyou for participating.

**APPENDIX E – AD FOR GENERAL POPULATION**

**Volunteers wanted…**

Regular smokers (i.e. 5 or more cigarettes per day) 18 years or older and with daily access to the internet are wanted to take part in a research study looking into what effect different methods of using nicotine patches have on

withdrawal symptoms.

During the study participants will be required to wear nicotine patches each day and to completely abstain from smoking. Participants will be required to complete a very brief (i.e. 1 min) online survey each day.

The study will take 29 days to complete, however there will only be 120 min of total face-to-face time with experimenters, spread over five weekly visits. Nicotine patches will be provided to participants free of charge. Participants will be reimbursed for out-of-pocket expenses.

The study is being conducted at the School of Psychology, University of Sydney.

If you are interested in participating please go to the following web address:

<https://sydneypsy.qualtrics.com/SE/?SID=SV_81CWMorqgtYv56p>

and complete the online study-eligibility questionnaire.

**APPENDIX F – AD FOR UNIVERSITY STUDENTS**

Regular smokers (i.e. 5 or more cigarettes per day) with daily access to the internet are wanted for a study investigating the effects that different methods of administering nicotine patches have on withdrawal symptoms. The study will require participants to wear nicotine patches each day and to completely abstain from smoking. Nicotine patches will be provided free of charge. The study will last for 29 days. Participants will be required to complete a very brief (i.e. 1 min) online survey each day. Participants will also be required to attend the Smoking Research Unit in Camperdown five times over the 29 days—once every 7 days—however total face-to-face time with experimenters will amount to approximately 120 min. Participants will receive 5 hours credit towards their research participation hours for taking part in this study.

**APPENDIX G – INSTRUCTION PACK (given to participants at baseline session)**

**Introductory Letter**

Dear Participant

Thankyou for taking part in this study. Thanks to your participation in this experiment we will be able to collect important data on the effects that different methods of nicotine patch administration have on withdrawal symptoms. By understanding this, hopefully we will be able to make recommendations to health professionals and drug companies about the optimal way to use nicotine patches, which will hopefully help smokers in future who are trying to quit to minimise stress and thus be more successful in their quit attempts.

If you follow the instructions contained in this information pack it will ensure not only that the data we collect is reliable and accurate—two things vital for meaningful research— but that your participation in this study is as comfortable, safe, and convenient as possible.

Below is a checklist of all the items that should be contained in this instruction pack. Please read over *all* these materials very carefully as they contain all the information you need to follow.

1. Participant Information Statement
2. Study Requirements
3. Instructions for application of patches
4. Study Schedule
5. Information about Side-effects and Medications that interact with nicotine patches
6. Emergency Contact Information.

If any of the items listed above are not in your instruction pack, please contact Llew Mills by email at [lmil8126@uni.sydney.edu.au](mailto:lmil8126@uni.sydney.edu.au) or by phone on 0421 032 614.

Yours Sincerely

The Research Team

**Appendix G.1. (Instruction Pack) – Participant Information Statement**

For Participant Information Statement see Appendix B

**Appendix G.2 (Instruction Pack) – Study Requirements**

**REQUIREMENTS FOR PARTICPATION IN**

**NICOTINE-PATCH STUDY**

Dear Participant

There are several important requirements that we have of you in order to continue to take part in this study. Please read these **very carefully** as they are vital both for the success of the study and for your own personal health and safety.

* 1. The most important is that you **don’t smoke**for the duration of the 28 days you are on nicotine patches. We would also ask you not to smoke e-cigarettes.
  2. Secondly we ask that you make sure **you apply *both* patches as instructed every day for the 28 days of the study**. Please look carefully at the labels on the patches each day to make sure you are applying the correct patch on the correct day. This applies to the people assigned to the Fixed group as well, since the labels will let you know how far you are through the study and thus how long you have to go (also because we need to make sure both groups are given exactly the same procedure in every way).
  3. When you remove the patches from the previous day and apply the new patches we ask that you **place these patches** **back into the pouches that the individual patches were wrapped in and return them (i.e. the used patches and the pouches) to us at each weekly face-to-face session** so that the researchers can verify that you have been applying the patches each day. At each return visit to the Smoking Research Unit we will collect these used patches and pouches from you and issue you with a new set of patches for the following week.
  4. Because many of the withdrawal symptoms abstinent smokers experience are psychological, we need to make sure that the symptoms you experience are due to you stopping smoking and not because you consumed some other kind of drug. Therefore we also ask that you consume **no psychoactive drugs of any kind during the 28 days of the study.** This includes both legal prescription drugs (such as anti-depressants, valium, xanax, ritalin etc.) and illegal drugs (such as marijuana, ecstasy, acid, speed, cocaine, heroin etc.). However you will be permitted to consume caffeine and alcohol in moderate amounts over the 28 days.
  5. We ask you **not to start** **any other form of treatment to help you stop smoking** over the course of the study. This includes:
     1. any types of nicotine replacement therapy such as nicotine gum, lozenges, inhalant or nasal spray
     2. drugs such as Chantix® or Zyban®
     3. any kind of self-help materials to quit smoking such as pamphlets, books, online tutorials, DVDs etc.
     4. any kind of counselling, such as hypnotherapy, phone counselling, cognitive behavioural therapy etc.
  6. We also ask that you **not enrol in another clinical trial for an experimental drug** during the study.

This study is aiming to help people by improving our knowledge of the best way to assist smokers such as yourself to stay quit for good, so please follow the requirements outlined above and hopefully we can work together to make sure the time and effort you put in helping us was well spent.

**APPENDIX G.3 (Instruction Pack) – APPLICATION OF PATCHES**

**INSTRUCTION FOR APPLICATION OF PATCHES**

Dear Participant

Below are the instructions for the safe use of your nicotine patches. Please read carefully and follow them. If you have any questions, or if you lose this document please contact Llew Mills by email at [lmil8126@uni.sydney.edu.au](mailto:lmil8126@uni.sydney.edu.au) or phone on 0421 032 614 and he will provide you with another.

* Apply two new patches every 24 hours to skin that is dry, clean, intact, non-irritated and hairless. Save pouch for disposing of the patch after use.
* Remove the backing from each patch and immediately press the patch onto your skin. Hold for 10 seconds.
* Wash your hands after applying or removing patch. Dispose of the old patches by folding the sticky ends of each patch together and replacing it in the pouch it came in. Researchers will collect these used pouches from you when you meet with them each week.
* Wear the patches for 24 hours.
* The used patch should be removed and a new one applied **to a different skin site**. For example if the patch from the previous day was on your upper arm, apply the new patch to your back or side, and vice versa.
* Old patches should be removed and new patches applied **at the same time each day**.
* Do not wear more than two patches at a time.
* Do not cut patch in half or into smaller pieces.
* Do not leave patches on for more than 24 hours because they may irritate your skin and lose strength after 24 hours.

**Important: Please ensure patches are stored out of reach of children**

Side-effects of nicotine patches are usually very mild; however if you or anyone who comes into contact with the patches experience any adverse symptoms please do not hesitate to contact Llew Mills on 0421 032 614 and/or call a doctor.

**APPENDIX G.4.1 (Instruction Pack) - Study Schedule for Aware Group**

Below is the schedule for the study. Stick it on your fridge or keep it by your bed and use a pen to tick the ‘Patches’ and ‘Online Survey’ box each day so you don’t forget. Make sure you cross reference the labels on the patches you apply each day with the schedule. Entries in bold mean you have to visit the Smoking Research Unit to pick up your patches for the next week.

|  |  |  |  |
| --- | --- | --- | --- |
| *Day* | *Event* | *Patches* | *Online Survey* |
| **Day 1** | **Baseline Session at Smoking Research Unit. First patches applied by experimenter.** |  |  |
| Day 2 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 3 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 4 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 5 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 6 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 7 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| **Day 8** | **First Return Visit to the Smoking Research Unit.** | ☐ | ☐ |
| Day 9 | Self apply 14-mg and 0-mg patch | ☐ | ☐ |
| Day 10 | Self apply 14-mg and 0-mg patch | ☐ | ☐ |
| Day 11 | Self apply 14-mg and 0-mg patch | ☐ | ☐ |
| Day 12 | Self apply 14-mg and 0-mg patch | ☐ | ☐ |
| Day 13 | Self apply 14-mg and 0-mg patch | ☐ | ☐ |
| Day 14 | Self apply 14-mg and 0-mg patch | ☐ | ☐ |
| **Day 15** | **Second Return Visit to the Smoking Research Unit.** | ☐ | ☐ |
| Day 16 | Self apply 0-mg and 7-mg patch | ☐ | ☐ |
| Day 17 | Self apply 0-mg and 7-mg patch | ☐ | ☐ |
| Day 18 | Self apply 0-mg and 7-mg patch | ☐ | ☐ |
| Day 19 | Self apply 0-mg and 7-mg patch | ☐ | ☐ |
| Day 20 | Self apply 0-mg and 7-mg patch | ☐ | ☐ |
| Day 21 | Self apply 0-mg and 7-mg patch | ☐ | ☐ |
| Day 22 | **Third Return Visit to the Smoking Research Unit.** | ☐ | ☐ |
| Day 23 | Self apply 0-mg and 0-mg patch | ☐ | ☐ |
| Day 24 | Self apply 0-mg and 0-mg patch | ☐ | ☐ |
| Day 25 | Self apply 0-mg and 0-mg patch | ☐ | ☐ |
| Day 26 | Self apply 0-mg and 0-mg patch | ☐ | ☐ |
| Day 27 | Self apply 0-mg and 0-mg patch | ☐ | ☐ |
| Day 28 | Self apply 0-mg and 0-mg patch | ☐ | ☐ |
| **Day 29** | **Final Return Visit to the Smoking Research Unit.** | **NO PATCH** | ☐ |

**APPENDIX G.4.2 (Instruction Pack) - Study Schedule for Unaware Group**

Below is the schedule for the study. Stick it on your fridge or keep it by your bed and use a pen to tick the ‘Patches’ and ‘Online Survey’ box each day so you don’t forget. Make sure you cross reference the labels on the patches you apply each day with the schedule. Entries in bold mean you have to visit the Smoking Research Unit to pick up your patches for the next week.

|  |  |  |  |
| --- | --- | --- | --- |
| *Day* | *Event* | *Patches* | *Online Survey* |
| **Day 1** | **Baseline Session at Smoking Research Unit. First patches applied by experimenter.** |  |  |
| Day 2 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 3 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 4 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 5 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 6 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 7 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| **Day 8** | **First Return Visit to the Smoking Research Unit.** | ☐ | ☐ |
| Day 9 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 10 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 11 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 12 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 13 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 14 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| **Day 15** | **Second Return Visit to the Smoking Research Unit.** | ☐ | ☐ |
| Day 16 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 17 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 18 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 19 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 20 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 21 | Self apply 14-mg and 7-mg patch | ☐ | ☐ |
| Day 22 | **Third Return Visit to the Smoking Research Unit.** | ☐ | ☐ |
| Day 23 | Self apply 0-mg and 0-mg patch | ☐ | ☐ |
| Day 24 | Self apply 0-mg and 0-mg patch | ☐ | ☐ |
| Day 25 | Self apply 0-mg and 0-mg patch | ☐ | ☐ |
| Day 26 | Self apply 0-mg and 0-mg patch | ☐ | ☐ |
| Day 27 | Self apply 0-mg and 0-mg patch | ☐ | ☐ |
| Day 28 | Self apply 0-mg and 0-mg patch | ☐ | ☐ |
| **Day 29** | **Final Return Visit to the Smoking Research Unit.** | **NO PATCH** | ☐ |

**Appendix G.5 – Side-Effects, Toxicity and Contraindications for use of Transdermal Nicotine Patches**

**What are the side-effects of nicotine patches?**

**Though side-effects of nicotine patches are rare (i.e. occurring in less than 1% of people) and usually mild. Notify researchers if you experience these side effects, either straight away by phone (there is a list of contact numbers in this instruction pack) or when you see them for your weekly visits. If they are severe or bothersome you should contact your doctor. Your pharmacist may be able to advise you on managing side effects.**

* anxiety
* constipation
* diarrhea
* dizziness
* fatigue
* headache
* insomnia (difficulty sleeping)
* irritability
* mild itching, burning, redness, or tingling in the area where the patch was applied
* upset stomach

**Although most of the side effects listed below don't happen very often, they could lead to serious problems if you do not seek medical attention.**

**Check with your doctor and notify researchers** **as soon as possible if any of the following side effects occur:**

* chest pain
* irregular heartbeat or heart palpitations
* leg pain
* severe stomach upset that does not go away
* skin rash or swollen skin
* skin redness caused by the patch that does not go away after 4 days

**Stop taking the medication and seek immediate medical attention if *any* of the following occur:**

* symptoms of a serious allergic reaction (such as hives, difficulty breathing, or swelling of the face and throat)

**Some people may experience side effects other than those listed.** Check with your doctor and notify researchers if you notice any symptom that worries you while you are taking this medication.

**Is there any chance of accidental overdose?**

Nicotine poisoning/overdose has occurred with nicotine patches in the past, however only through the deliberate misuse of them, either by simultaneous application of a large number of patches (e.g. 8-11 patches at once) or by combining them with multiple alternative sources of nicotine (e.g. gum and cigarettes). When used as directed there have been no reported cases of poisoning. We recommend that you use these patches as instructed by the experimenters.

You should however **keep the patches out of reach of children** for a it takes much less nicotine for a child to overdose than an adult and children may not follow the instructions for application.

**Symptoms of overdose**

* abdominal or stomach pain
* cold sweat
* confusion
* convulsions (seizures)
* disturbed hearing and vision
* drooling
* extreme exhaustion
* pale skin
* rapid heartbeat
* tremors

If an overdose occurs, please do not hesitate to call an ambulance.

**What other drugs could interact with Nicorette Patch?**

**There may be an interaction between nicotine patches and any of the following:**

* acetaminophen
* adenosine
* benzodiazepines (e.g., oxazepam)
* caffeine
* furosemide
* imipramine
* insulin
* labetalol
* peginterferon alfa-2b
* phenylephrine
* prazosin
* propranolol
* theophylline

**If you are taking any of these medications, speak with your doctor or pharmacist.** Depending on your specific circumstances, your doctor may want you to:

* stop taking one of the medications,
* change one of the medications to another,
* change how you are taking one or both of the medications, or
* leave everything as is.

**An interaction between two medications does not always mean that you must stop taking one of them.** Speak to your doctor about how any drug interactions are being managed or should be managed.

**Medications other than those listed above may interact with this medication.** Tell your doctor or prescriber about all prescription, over-the-counter (non-prescription), and herbal medications you are taking. Also tell them about any supplements you take. Since caffeine, alcohol, the nicotine from cigarettes, or street drugs can affect the action of many medications, you should let researchers know if you use them.

**APPENDIX G.6 – Contact Information**

Dear Participant

If you have any questions about the study or its procedures, or in the unlikely event of a medical emergency relating to the study please do not hesitate to contact the Primary Investigator, Llew Mills, whose details are supplied below, at any time, day or night. Also supplied are the contact details of Llew’s supervisors in the study, Dr Ben Colagiuri and Professor Renee Bittoun, who will be available to answer general questions about the study. Should you experience a medical emergency, call 000 and ask for an ambulance. Also provided are the address and phone numbers of several hospitals in the local area.

**Primary Investigator (Emergency Contact)**

Mr Llewellyn Mills

PhD Candidate

Room 310, Griffith Taylor, A19

University of Sydney

NSW, Australia, 2006.

Email: [lmil8126@uni.sydney.edu.au](mailto:lmil8126@uni.sydney.edu.au)

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Email: [bittounr@med.usyd.edu.au](mailto:bittounr@med.usyd.edu.au)

Telephone: +61 2 93510816 Fax: +61 2 9351 0731

Dr Ben Colagiuri

Lecturer

University of Sydney

Room 444, Brennan MacCallum, A18

University of Sydney

NSW, Australia, 2006.

Email: [ben.colagiuri@sydney.edu.au](mailto:ben.colagiuri@sydney.edu.au)

Telephone: +61 2 9351 4589 Fax: +61 2 9351 5223

**Medical Emergency Information**

Dial **000** for emergency assist (ambulance, police, fire)

Emergency Department

Royal Prince Alfred Hospital

Missenden Road

Camperdown NSW, 2050.

Telephone (02) 9515 6111

Emergency Department

St Vincent’s Hospital

390 Victoria St

Darlinghurst NSW, 2010.

Telephone (02) 8382 1111

Emergency Department

Prince of Wales Hospital

320-346 Barker St

Randwick, NSW, 2031.

Telephone (02) 9382 2222

**Appendix H.1 Timeline of Procedure for Proposed Nicotine-Patch Dose-Reduction Study**

|  |  |
| --- | --- |
| Event | Description |
| **Online Screening** | Participants answer ad or flyers directing them to an online screening questionnaire where they will be asked for basic demographic data such as age and gender and for number of cigarettes smoked per day.  If participants meet initial eligibility criteria (i.e. ≥5 cigarettes smoked per day, ≥18 yrs-old, and daily internet access) they will be emailed and asked to attend a screening and baseline and admission session. |
| **Baseline Session**  Day 1  Estimated time: 60 min | At screening and baseline session participants will first be given a CO reading to verify that they are regular smokers. A reading of <10 ppm will be grounds for exclusion from the study. They will then be asked further screening questions to determine if they meet the following eligibility criteria:   1. no prior history of cardiovascular disease, hypertension, or diabetes 2. not pregnant or breastfeeding 3. no prior history of chronic dermatological disorders 4. no prior history of moderate to severe allergies 5. have not been on nicotine replacement therapy of any kind in the 3 months prior to commencement of the study 6. are not regular users of any psychoactive drugs, legal or illegal, other than caffeine or alcohol 7. are not currently diagnosed with a mental disorder   If participants meet all eligibility criteria they will be given Participant Information Statement and asked to sign a Participant Consent Form (in which they will be asked to consent to being contacted at 1 week, 1 month, and 3 months to complete a 2-min online follow-up questionnaire).  Upon giving consent participants will be asked to complete:   1. a *Tobacco History Questionnaire* (Hendricks & Leventhal, 2013) 2. the *Fagerström Test for Cigarette Dependence* (FTCD; Fagerström, 2012) 3. a 13-item questionnaire aimed at ascertaining participants’ expectancies for experiencing withdrawal effects and ease of quitting. This questionnaire will be comprised of the *Withdrawal* and *Optimistic Outcomes* subscales of the *Smoking Abstinence Questionnaire* (SAQ; Hendricks et al. 2011) 4. the 4-item *Thoughts About Abstinence Questionnaire* (Hall et al. 1990)   Participants will then be   1. randomly allocated to experimental condition 2. shown how to apply their first patches 3. given instructions on how and when to apply patches in the following weeks 4. supplied with an instruction kit including emergency contact info, dosing schedule, study requirements (i.e. restriction criteria) etc. 5. shown how to complete the daily online *Withdrawal and Abstinence Questionnaire* on their iPhone or by computer 6. given contact information of researchers if there are any problems 7. given their first set of 12 nicotine patches to apply at home 8. asked to completely refrain from smoking for the duration of the study 9. asked to return at the same time in 7 days time to receive their next set of 7 patches |
| **1st, 2nd, and 3rd Return Visit**  Day 8, 15, and 22 of study  Estimated time: 10 min per session | Participants will:  1) be given a CO reading and have the wrappers for their twelve nicotine patches collected   1. be given a compliance questionnaire, asking participants to provide details about any difficulties they may have had with study compliance 2. have their first two patches of the 7-day period applied by the researcher 3. be given the remaining 12 patches for the week 4. be asked to return in 7 days time   The final patches of the study (the final of the 12 patches given to participants on their 3rd visit) will have labels reading ‘Congratulations!! The last 6 days you have been on 0-mg placebo patches. Therefore you have been *completely* nicotine-free for a week. Please make one more visit to see the researchers tomorrow and then you will be finished with the study – and smoking – for good! You will not be required to wear these final two patches’. |
| **Final Visit/Debrief**  Day 29  Estimated time: 20 min | Participants will attend a final debriefing session where they will:   1. be given a short questionnaire probing them for possible knowledge about whether the dosing information on patch labels was accurate 2. be told the true dosing regimen (for participants in the Aware condition this will not be necessary, as their labels accurately reflected their true dose throughout the study). 3. be given a final CO reading 4. be asked to complete a final online withdrawal questionnaire. 5. be given a debrief statement outlining the true purpose, design and procedure of the study. 6. be asked if they are willing to answer questions about their abstinence status in 1 week, 1 month, and 3 month’s time. |
| **Follow-up**  1 week, 1 month and 3 months after end of study.  Estimated time: 2-min per questionnaire | At 1 week, 1-month and 3-month’s time participants will be sent an email with a link to an online questionnaire asking if they have remained abstinent in the intervening period since the study ended. If they answer no they will be asked to estimate when they began to smoke again and how many cigarettes a day they are currently smoking.  If participants do not fill in the questionnaire they will be contacted by phone. |

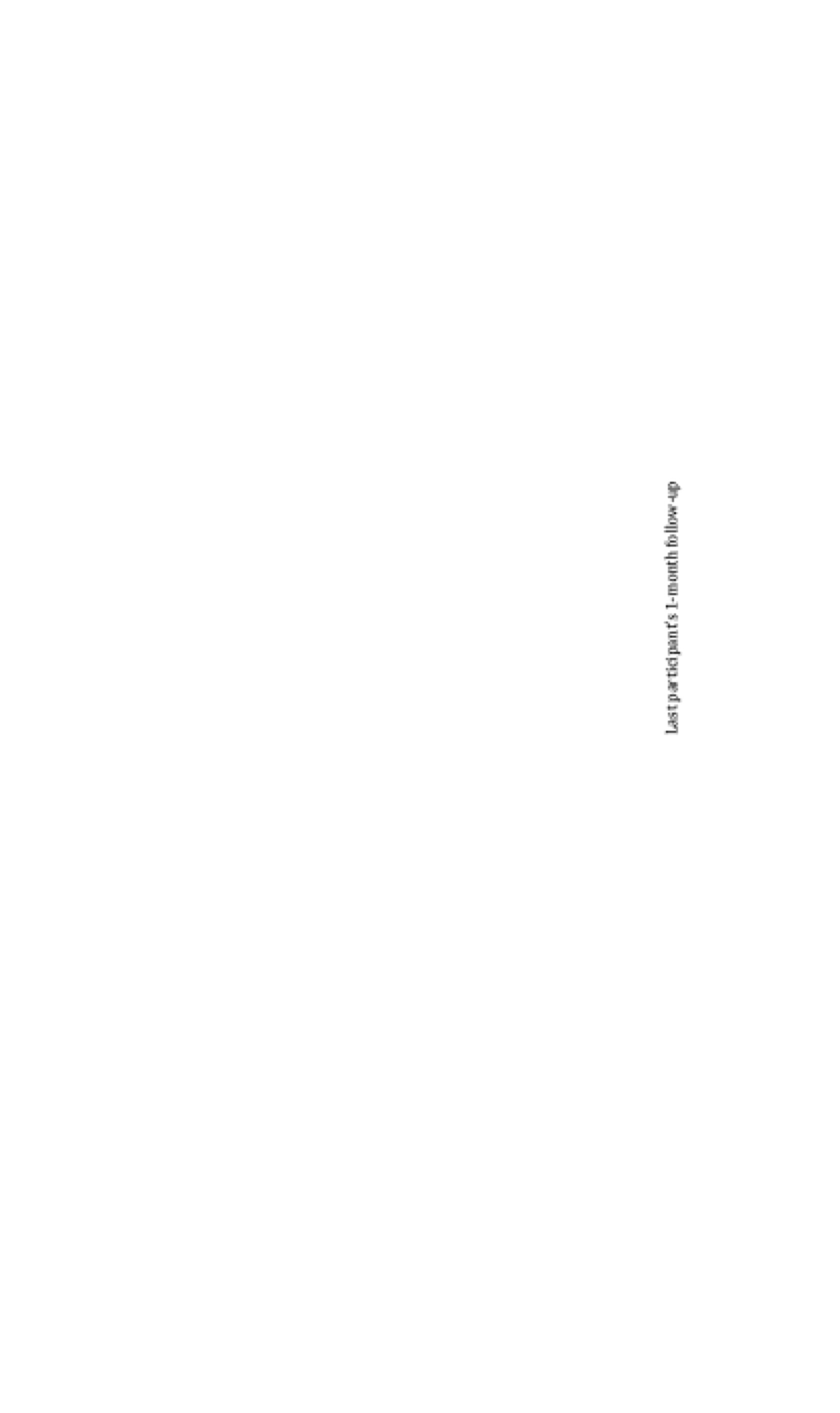
First Participant attends baseline session

Last participant’s final/debrief session

Second semester begins. Participants recruited from USyd student body and general population

Aug 5, 2014

Aug 5, 2014

December 1, 2014

July 29, 2014

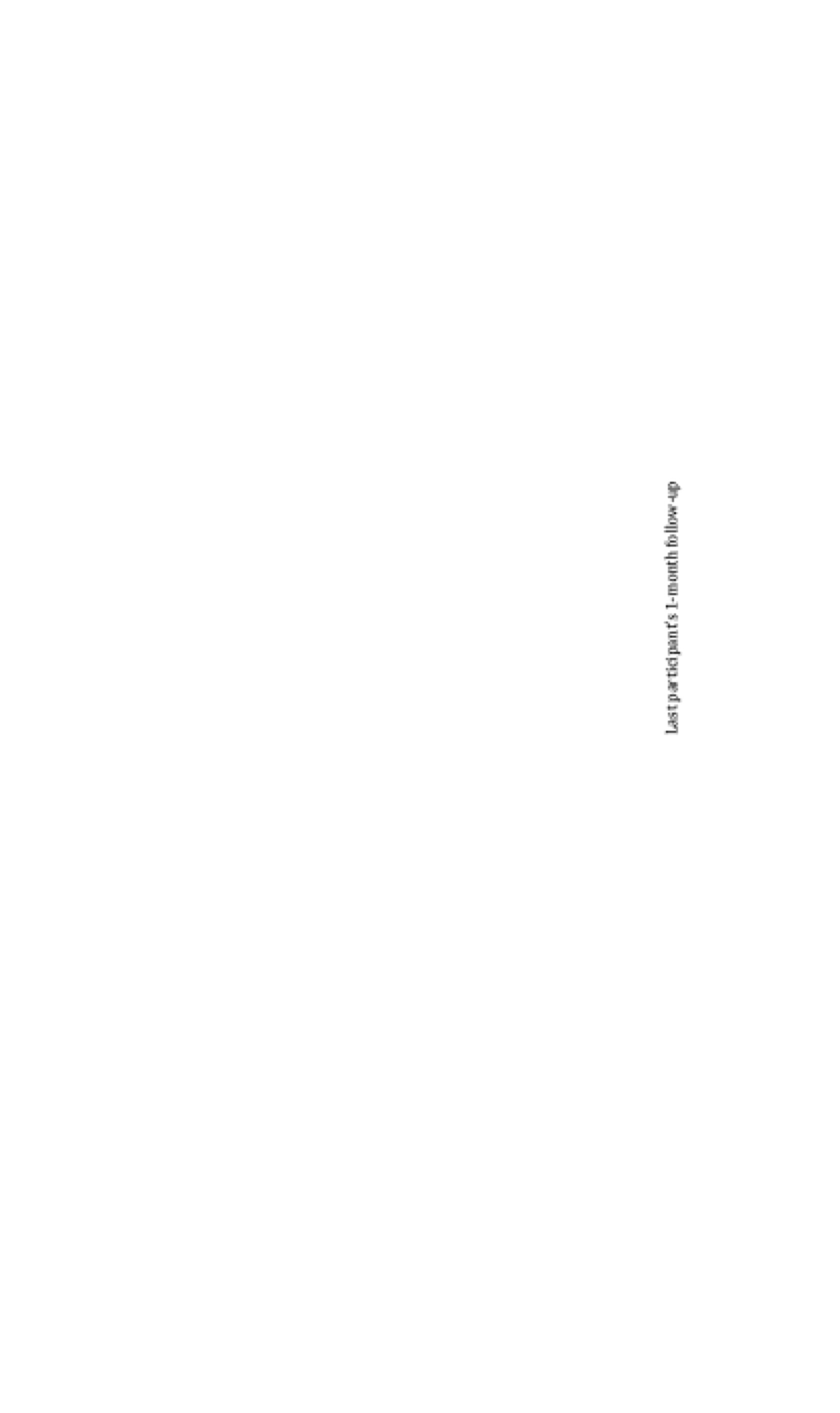
Nov 1, 2014

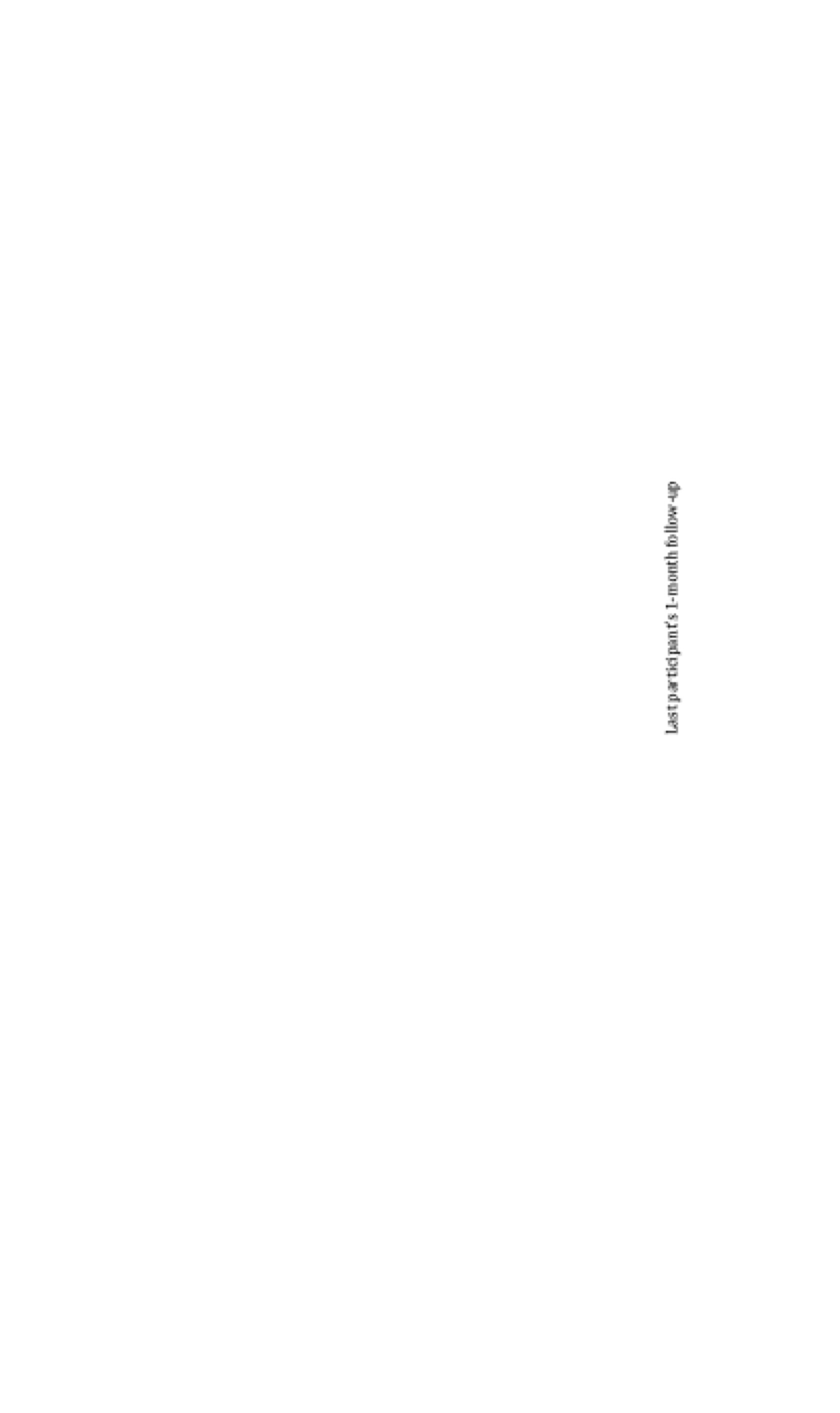
Last participant’s 1-week follow-up

Last participant’s 1-month follow-up

Last participant’s 3-month follow-up

Final Report and Submission of Manuscript for Publication

February 1, 2015

February 15, 2015

**Appendix H.2. Estimated Timeline for Milestones in Withdrawal Expectancy Study**



0

21 mg

14

14

14

14

14

0

0



Day 28

14 mg

7 mg

0 mg

7

0

7

7

7

7





Day 22-27

Day 15-21

Day 8-14

Day 1 - 7



Congratulations!!

The last 6 days you have been on 0-mg placebo patches. Therefore you have been *completely* nicotine-free for a week.

14

Actual

Dose

Aware

Unaware

7

**Appendix I. Design for Nicotine-Patch Dose-Reduction Regimen**

*Note: the actual combination of 14-mg, 7-mg and placebo patches in the Unaware group will be the same as the Aware group.* *The above indicates what the labels on their patches will read. Though dose will be reduced on average every seven days, the exact duration between dose titrations will be different for each participant. For example a participant could spend 6 days on 21 mg, 8 days on 14 mg, 9 days on 7 mg and 5 days on placebo. Thus average titration will be 7 days across the study.*

1. It should be noted however that since open/hidden designs involve the surreptitious administration and/or discontinuation of a drug or treatment, they are only suited to drugs or treatments whose administration, interruption, or reduction can be successfully concealed, which is a very restricted range of treatments. [↑](#footnote-ref-1)