Research Proposal

Comparing the effectiveness of nicotine patch with gum versus nicotine patch alone in smoking cessation in Hong Kong primary care clinics

Introduction

Cigarette smoking is the leading preventable cause of mortality, responsible for nearly six million deaths worldwide (WHO, 2011). Smoking related-diseases kill 1 in 10 adults globally. By 2030, if current trends continue, smoking will kill 1 in 6 people. In Hong Kong, smoking kills 5700 persons per year. Smoking is related to cardiovascular diseases, stroke, chronic obstructive pulmonary disease and many kinds of cancers. Thus, smoking cessation is associated with substantial health benefits for all smokers (Rigotti, 2002).

Pharmacotherapy in smoking cessation plays an important role in reducing the withdrawal symptoms, thus, facilitating clients to stop the habit of smoking. First line pharmacotherapies for smoking cessation include varenicline, bupropion and NRT. In a recent meta-analysis (Mills et at, 2012), Varenicline was the only treatment demonstrating effects over the other options including high dose nicotine patch, combined NRT and bupropion. However, according to FDA report 2008, there is a possible association between suicidal events and the use of varenicline. According to our local pilot study in 2011 presented in Hospital Authority Convention (Chan et al, 2011), the smoking cessation rate after a 12-weeks course of Varenicline can be as high as 43%. However, 20% of smokers experienced side effects such as gastrointestinal upset, dizziness and headache. As a result, these patients could not complete the course of therapy.

Nicotine replacement therapy (NRT) aims to provide nicotine to smokers without them smoking tobacco, thus, helping them to break the smoking habit. It is a safe and effective intervention. Currently, different preparations are available for smokers: transdermal patch, gum, and lozenge as well as combination therapy.

The efficacy of any monotherapy is limited (Ebbert et al, 2010) especially in heavy smokers due to significant withdrawal symptoms. Combination NRT provides a stable baseline nicotine level by means of nicotine patch plus intermittent usage of short acting NRT e.g. gums, lozenges or inhalers for withdrawal symptoms. Combined NRT is associated with higher salivary continine concentrations and lower withdrawal scores (Fagerstrom et al, 1993). Randomized controlled trials (Smith et al, 2009; Piper et al, 2009) have also shown that the 6-month post quit cessation rate of combination therapy of nicotine patch and lozenge was 26.9%. Megan *et al* (2009) also showed that combination nicotine therapies were superior to nicotine monotherapies. Trials of combining various NRTs (Stead et al, 2008) did not report that combination treatment produced increased adverse events.

Yet, data on benefits of combined NRT in smoking cessation are lacking in Hong Kong primary care clinics. Thus, this study serves as the first territory wide study across all seven clusters in Hospital Authority to compare the effectiveness of combined NRT with single NRT in primary care smoking cessation clinics. The results of this study can help enhance the workflow in our smoking cessation framework, which in turn, can further enhance smoking cessation. Such improvement can greatly help reduce the total costs on healthcare in a long run.

Literature Review

Pharmacotherapy in smoking cessation plays an important role in reducing the withdrawal symptoms, thus, facilitating clients to stop the habit of smoking. First line pharmacotherapies for smoking cessation include varenicline, bupropion and nicotine replacement therapy.

Varenicline

Varenicline is a partial agonist at the alpha-4 beta-2 subunit of the nicotinic acetylcholine receptor, the receptor that appears to produce the reinforcing effects of nicotine and leads to nicotine dependence (Coe et al, 2005; Hays et al 2008; Henningfield et al, 2005). A meta-analysis (Fiore et al, 2008) done for the US Preventive Health Service practice guidelines found that varenicline increased the odds of quitting three-fold compared to placebo (OR 3.1, 95% CI 2.5-3.8) and produced a quit rate of 33 percent at six month follow-up.

In 2008, the FDA reported "a possible association between suicidal events and the use of varenicline" based upon review of post-marketing reports (FDA newsletter, 2009). Patients should be monitored for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, suicidal ideation, and suicide attempts.

Nicotine replacement therapy (NRT)

NRT aims to provide nicotine to smokers without them smoking tobacco, thus, helping them to break the smoking habit. Currently, different preparations are available for smokers: transdermal patch, gum, and lozenge as well as combination therapy.

Combination nicotine replacement therapy

Nicotine combination therapy involves a nicotine patch plus a short-acting nicotine replacement therapy such as gum, inhaler or lozenge. The nicotine patch is the primary NRT product to control baseline nicotine withdrawal symptoms. A short-acting form of NRT helps to control cravings and withdrawal symptoms during the day on an as needed basis. The choice of a short-acting agent depends on patient preference. Randomized controlled trials (Smith et al, 2009; Piper et al, 2009) have shown that the 6-month after quitting cessation rate of combination therapy of nicotine patch and lozenge was 26.9%. A meta-analysis done by Fiore et at (2008) (see Table 1) showed that 6-month after quitting cessation rate of a combination therapy with patch with gum/spray was 36.9%. Both rates are higher than single nicotine replacement therapy.

Table 1.

Preparation	**No of arms**	**Estimated abstinence rates at 6 months post quit**
Placebo	80	13.8
Nicotine patch (6-14 weeks)	32	23.4 (21.3-25.8)
Nicotine gum (6-14 weeks)	15	19.0 (16.5 – 21.9)
Nicotine patch + ad lib gum/spray	3	36.5 (28.6 – 45.3)

With the current evidence from overseas studies, both varenicline and combined nicotine replacement therapy are the two most effective smoking cessation therapies. However, there is not without limitations when using varenicline. There is a possible association of varenicline with neuropsychiatric symptoms and should be best avoided in these patients. In addition, a certain proportion of patients report side effects from varenicline (Chan et al, 2011). On the other hand, not much side effects have been reported with combined nicotine replacement therapy and this regimen can also be used in patients with psychiatric illnesses. If combined nicotine replacement therapy is shown to be more effective than single NRT in our locality, it could be widely used to help further improve the smoking cessation rates.

Research questions:

1. How effective is combination nicotine replacement therapy compared to single nicotine replacement therapy in Chinese population?

Hypothesis:

Nicotine patch with gum is more effective than nicotine patch alone in smoking cessation.

Objective:

To compare the effectiveness of nicotine patch with gum and nicotine patch alone in Hong Kong primary care smoking cessation clinics

Methods:

This is an interventional, non-blinded randomized controlled trial.

Participants:

Inclusion criteria:

Current smokers, who smoke 10 or more cigarettes a day, will be recruited from general outpatient clinics.

Exclusion criteria:

The following smokers will be excluded:

- unstable angina,
- severe cardiac arrhythmia,
- recent acute myocardial infarction or cerebrovascular accident in preceding 3 months (McRobbie and Hajek, 2001),
- below 18 years old,
- being pregnant or on breast-feeding,
- unable to use gum,
- with a previous history of failure to NRT
- hypersensitivity to nicotine

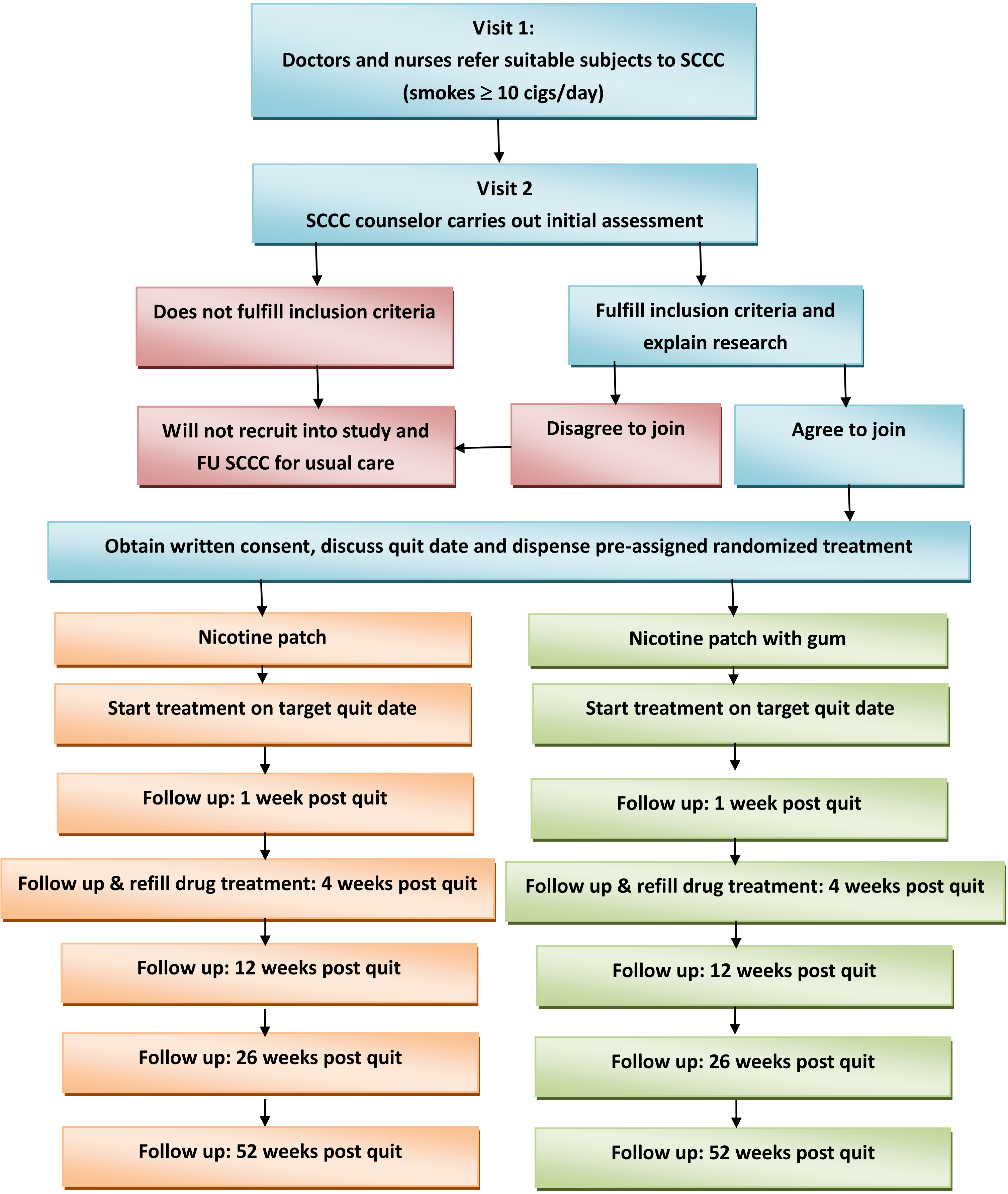
Recruitment procedure:

The study will be carried out in the smoking cessation clinics located in the 5 clusters (Table 2): Hong Kong East, Kowloon East, Kowloon Central, New Territories East and New Territories West Clusters. Doctors and nurses from the involved clinics will refer motivated patients to smoking cessation counselors at the sites. In the initial assessment, smoking cessation counselor will assess their smoking history. When these patients meet the inclusion criteria, smoking cessation counselors will explain the research to these patients and recruit them. Written consent will be obtained from these patients. A statistician who is not involved in any part of the study independently randomized participants by using a predetermined random table generated by Microsoft Excel 2002. The randomization number generated will be assigned to one of the two treatments: combined nicotine replacement therapy or single nicotine replacement therapy. Patients will then be followed up at 1 week, 4 weeks, 12 weeks, 26 weeks and 52 weeks after quit day (Diagram 1).

Table 2. A List of involved clinics for this study

Clusters	Clinics
Hong Kong East	1. Anne Black GOPC 2. Chai Wan GOPC 3. Sai Wan Ho GOPC 4. Shau Kei Wan JC GOPC 5. Wan Tsui GOPC1
Kowloon East	1. Tseung Kwan O JC GOPC 2. Ngau Tau Kok JC GOPC
Kowloon Central	1. Queen Elisabeth SCCC 2. Central Kowloon Heatlh Centre 3. Yau Ma Tei General Outpatient clinic
New Territories East	1. Fanling family medicine centre, 2. Wong Siu Ching family medicine centre 3. Tai Po Jockey Club GOPC 4. Ma On Shan family medicine centre 5. Lek Yuen GOPC
New Territories West	1. Tuen Muen CCC/Yan Oi GOPC 2. Tin Shui Wai Health Centre 3. Tin Shui Wai CHC 4. Yuen Long JC GOPC

Diagram 1. Details of workflow and study timeline



Intervention:
Participants receive open labeled medications. NRT will be given by counselors for 8 weeks.

Control group:
In this study, control group receives usual counseling and single NRT i.e. nicotine patch

Intervention group:
The intervention group receives usual counseling and combined NRT consisting of nicotine patch and gum.

Table 3. Treatment arms

1	Combined nicotine therapy i.e. nicotine patch + gum	Long acting nicotine patch + short acting nicotine gum (appendix 1 on prescription guideline on NRT)
2	Single nicotine therapy i.e. nicotine patch	Nicotine patch (appendix 1 on prescription guideline on NRT)

Potential side effects from interventions (Please see Appendix 1 for details)

Intervention	**Potential side effects**
Nicotine gum	● If the gum is chewed continuously and quickly, side effects such as throat and stomach irritation, indigestion or hiccups may occur
Nicotine patch	● May cause redness, burning or stinging feeling or skin rash
Combined nicotine gum and patch	● Same as above

Trials of combining various NRTs (Stead et al, 2008) did not report that combination treatment produced increased adverse events. Any adverse effects from treatment will be reported to the investigators and patients will be advised to stop the intervention.

Sample size Calculation:

According to a meta-analysis in 2008, smoking cessation rates (26 weeks post quit) for combined nicotine therapy is about 36.5% and that of nicotine patch is 23.4%. Based on the sample size calculator provided from Chinese university, the sample size could be calculated as below:

Suppose it is of interest to test for equality of the smoking cessation rates of combined NRT as compared to single NRT. Considering that the true mean 26 weeks post quit cessation rate of combined NRT and single NRT are given as θ_1=36.5% and θ_2=23.4%, respectively. Then, the required sample size with equal allocation (r=1) to achieve a 90% power (β=0.1) at α=0.05 will be n1=n2=252.

However, it is important to take into account the response rate, eligible rate, and the prevalence. Hence, the sample size has to be adjusted according to these. Assuming only 90% of these patients are eligible to join according to the exclusion criteria, then the actual sample size should be 252/0.9 = 280. Then to get the effective sample size (n=56), each cluster should be expected to enroll 40 smokers per arm over a period of nine months. A total of 280 smokers per arm would be required.

This means the sample size for each clinic site will be:

Cluster	**Nicotine patch + gum (n1=280)**	**Nicotine patch (n2=280)**
Hong Kong East	56	56
Kowloon East	56	56
Kowloon Central	56	56
New Territories East	56	56
New Territories West	56	56
Total	**280**	**280**

Smoking status

In this study, carbon monoxide (CO) level would be obtained to confirm smoking status. It is simple to measure and is relatively inexpensive. It can be measured in expired air by CO meter in the clinics. With reference from SRNT (2002), a CO level of <8pp in expired air will be used as a cut off concentration to distinguish non-smokers from smokers.

Primary Outcome:

7-day point-prevalence abstinence assessed at 1 week, 4 weeks, 12 weeks, 26 weeks and 52 weeks after the quit date. In the study, the date of recruitment i.e. date of initial assessment will be used as quit date.

Secondary Outcome:

Demographic factors and co-existing medical conditions will be collected for analyzing association with cessation rates. Adverse events related to the intervention will be recorded and analysed.

Statistical analysis:

All analyses will be carried out on an intent-to-treat basis. Data will be extracted from notes from Smoking Cessation Programme. Statistical analyses will be done using the Statistical Package for Social Sciences (SPSS). All statistical significance tests are two-tailed, and the level of significance will be taken as $p < 0.05$. Longitudinal analysis will be conducted to compare the effectiveness between the two drugs over time (Wiley, 2011).

Data collection and patient confidentiality:

In order to safeguard patient confidentiality, patients' data will be collected by counselors and will be stored in Clinical Management System (CMS) which can only be accessed by the doctors and smoking cessation counselors who have access rights to CMS in the centre.

Written informed consent:

Potential benefits and risks of the study will be explained to participants by counselors. Written consent will be obtained from participants in written form. Participants would be allowed to withdraw from the study at any time with no consequences to their usual treatment.

Primary responsibility

Investigators from Hospital Authority will be solely responsible for the primary responsibilities of the research as listed in the Clinical Research handbook (Hospital Authority, 2010).

Application for Certification of Clinical Trial

For the purpose of regulatory compliance, a Certificate for Clinical Trial ("CTC") shall be obtained before initiation of any clinical study of any pharmaceutical product. An application for a CTC shall be submitted to the Pharmaceutical Registration Section of the Hong Kong Department of Health ("DOH"). It could take up to 3 months for approval and should be done at the same time as application for ethics committee approval.

Application for Ethics Committee approval

Application for approval from Ethics Committee will be done separately by individual cluster.

Conflicts of interests

Nil

Schedule of the research

0 - 4 weeks Sep 2013	Liaison with counsellor and doctor in charge from each cluster, recruitment of research assistant
5 - 39 weeks Oct 2013 – Jun 2014	Patient recruitment
40 – 92 weeks Jul 2014 - Jun 2015	Ongoing study with patients being followed up according to protocol
92-104 weeks Jul 2015 – Sep 2015	Data analysis and report preparation

This study complies with Declaration of Helsinki and ICH-CGP.

References:

1. Casegrande, Pike and Smith (1978), Biometrics 34:483-486.
2. Coe JW, Brooks PR, Vetelino MG, et al. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. J Med Chem 2005; 48:3474.
3. Chow, Shao and Wang, *Sample Size Calculations In Clinical Research*, Taylor & Francis, NY. (2003) Pages 88-89
4. Chan LP, Leung KW, Wong PH, Cheung KW, Lam TA, Li KTP. Efficacy of Varenicline in enhancing smoking cessation in primary care clinic. HA Convention 2011.
5. Clinical Research. Management and compliance at study sites. A practical handbook for investigators, clinical research personnel and administrators of the Hong Kong Hospital Authority, 2010.
6. Ebbert JO, Hays T, Hurt RD. Combination Pharmacotherapy for stopping smoking: what advantages does it offer? Drugs. 2010; 70:643-50.
7. Fagerstrom KO, Schneider NG, Lunell E. Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. Psychopharmacology (Berl) 1993; 111(3): 271-7.
8. Fiore, MC, Jaen CR, Baker TB, et al. Clinical Practice Guideline. Treating Tobacco Use and Dependence: 2008 update. US Department of Health and Human Services, May 2008.
9. Fitzmaurice Garrett M. Applied Longitudinal Analysis (2nd edition). Wiley Series in Probability and Statistics 2011 (ISBN-10:0470380276, ISBN-13:9780470380277).
10. Flesis J.L., *Statistical Methods for Rates and Proportions (2nd edition)*. Wiley: New York, 1981
11. Hays JT, Ebbert JO. Varenicline for tobacco dependence. N Engl J Med 2008; 359:2018.
12. Henningfield JE, Fant RV, Buchhalter AR, Stitzer ML. Pharmacotherapy for nicotine dependence. CA Cancer J Clin 2005; 55:281.
13. Hong Kong Thematic Household Survey report 48
14. Leung M; Chan LP; Wong CL; Lam A; Li KTP. Smoking cessation - are we targeting at the right group of patients. Poster presentation, Hospital Authority Convention, 2011.
15. McRobbie H; Hajek P. Nicotine therapy in patients with cardiovascular disease: guideline for health professionals. Advice. 2001; 96: 1547-1551.
16. Mills EJ, Wu P, Lockhart I, Thorlund K, Puhan M, Ebbert JO. Comparsions of high dose and combination NRT, varenicline, and bupropion for smoking

cessation: A systemic review and multiple treatment meta-analysis. Annals of Med, 2012: early online: 1-10.

17. Piper ME; Smith SS; Tanya R. Schlam; Michael C. Fiore; Douglas E. Jorenby; David Fraser; Timothy B. Baker. A Randomized Placebo-Controlled Clinical Trial of 5 Smoking Cessation Pharmacotherapies. *Arch Gen Psychiatry.* 2009*;* 66 (11): 1253-1262.
18. Rigotti NA. Clinical practice. Treatment of tobacco use and dependence. N Engl J Med 2002; 346:506.
19. Sample size calculator. Chinese Univeristy. Available at : http://www.cct.cuhk.edu.hk/stat/Proportions.htm (Accessed on 14 Aug 2012)
20. SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. Nicotine Tob Res. 2002; 4(2):149-159.
21. Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD000146. DOI: 10.1002/14651858.CD000146.pub3.
22. Smith SS; Danielle E. McCarthy; Sandra J. Japuntich; Bruce Christiansen; Megan E. Piper; Douglas E. Jorenby; David L. Fraser; Michael C. Fiore; Timothy B. Baker; Thomas C. Jackson. Comparative Effectiveness of 5 Smoking Cessation Pharmacotherapies in Primary Care Clinics. Arch Intern Med. 2009; 169(22): 2148-2155.
23. The smoking cessation aids varenicline (marketed as Chantix) and bupropion (marketed as Zyban and generics): suicidal ideation and behavior. FDA Drug Safety Newsletter 2009; 2:1. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/ucm107318.pdf (Accessed on 11 Aug 2012).
24. World Health Organization Report on the Global Tobacco Epidemic, 2011: Warning about the dangers of tobacco. World Health Organization, Geneva 2011. http://whqlibdoc.who.int/publications/2011/9789240687813_eng.pdf (Accessed on 11 Aug 2012).

Appendix 1. Prescription guideline on Nicotine Replacement Therapy

Item	Pros and cons	Preparations	Dosing Recommendations
Nicotine Patch	Pros: ● Easy to use ● Long acting Cons: ● Slower onset ● May cause redness, burning or stinging feeling or skin rash	● 24 hours: 7, 14, 21 mg	24 hours patch: ● ≥40 cpd = 42mg/day ● 21-39 cpd = 28-35mg/day ● 10-20 cpd = 14-21mg/day ● <10 cpd = 14mg/day Maximum dosage: 42mg/day Adjust dosage according to withdrawal symptoms, cravings and discomfort. Initial dose for 4-6 weeks, then taper every 2-4 weeks in 7-14mg steps. If patient develops irritative symptoms at night, can take off the patch during sleep.
Nicotine Gum	Pros: ● Easy to use ● Faster delivery, for short acting use Cons: ● Should not eat or drink 15 mins before use ● Frequent to ease off cravings ● If the gum is chewed continuously	● 2mg, 4mg ● In original/mint flavours	Based on time to first cigarette of the day: ● If <30mins = 4mg ● If >30mins = 2mg Based on cigarettes/day ● ≥20 cpd = 4mg ● <20 cpd = 2mg Initial dosing is 1-2 pieces every 1-2 hrs (10 to 12 pieces/day)

	and quickly, side effects such as throat and stomach irritation, indigestion or hiccups may occur		
Item	**Pros and Cons**	**Preparations**	**Dosing Recommendations**
Combination Patch + gum	Pros: ● More effective than monotherapy Cons: ● Including the side effects from nicotine gum and patch	As above	● Prescribe patch dosage according to number of cigs/day and add 2mg gum every 1-2 hours as needed when withdrawal symptoms occur. ● Step up dose of patch if frequent use of gum is needed.

References: 1) Mayo Clinic NDC tobacco dependence treatment medication summary; 2) Department of Health; 3) Mils et al , Adverse events associated with nicotine replacement therapy (NRT) for smoking cessation. A systematic review and meta-analysis of one hundred and twenty studies involving 177.390 individuals, *Tobacco Induced Diseases* 2010, 8:8