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Australia and New Zealand Horizon Scanning Network

Horizon scanning report

The provision of free nicotine patches within smoking cessation programmes

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Te Whare Wānanga o Otago

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Executive Summary

Objective

All forms of nicotine replacement therapy (NRT) can help people quit smoking, almost doubling long-term success rates and nicotine patches appear to be a well tolerated aid for some groups of smokers wishing to quit. It has been suggested that altogether removing any financial barriers to access may further increase the uptake of this quitting aid. This report summarises the evidence for the provision of free nicotine patches within smoking cessation programmes.

Methods

The literature was searched using the following databases: Medline, Embase, Cinahl, PsychInfo, Current Contents, Web of Science, the Cochrane Register of Controlled Trials and the Cochrane Database of Systematic Reviews. Other electronic sources including a range of Internet sites were also searched. Only published material English language material was considered. Studies were retrieved and included in this summary if they explicitly mentioned the free provision of NRT in their title or article abstract.

Results

A total of 11 studies that have used control groups and randomisation to intervention group were found but not all of these were directly relevant when examined more closely. A further 12 pseudo randomised controlled trials or comparative studies were also profiled and many of these studies directly compared free NRT with usual care. Only a small number of studies (n=2) were identified that considered issues of cost effectiveness for free NRT.

Conclusions

The existing evidence is inadequate for drawing conclusions about whether the provision of nicotine patches free of charge increases their uptake compared with providing potential quitters with a prescription, subsidy or voucher to purchase patches at a reduced price. While free NRT is more effective than placebo, it is not clear whether the observed effect is over and above what it would be if the NRT was provided at cost to the user. Only one trial has directly compared a group receiving a free supply of patches to a group receiving a prescription and study design and response rate issues limited the conclusions that could be made. Future provision of free NRT should preferably be piloted within the context of a randomised controlled trial. Data on its effectiveness in increasing the uptake of NRT as part of smoking quit attempts (given its proven effectiveness in increasing quit success rates) could then be obtained and compared with partly subsidised or full-cost NRT.

Prepared by New Zealand Health Technology Assessment, NZHTA, this horizon scanning report reviewed the evidence for improvement in the overall effectiveness of smoking cessation programmes using nicotine patches for nicotine replacement therapy (NRT) **specifically when the patches are provided free** to the patient.

Twenty three studies were identified that addressed aspects of the provision of nicotine replacement without cost. However, only one study directly compared a group receiving a free supply of patches with a group receiving patches by prescription (Dey et al. 1999). This study was considered to have methodological flaws. No clear conclusion could be drawn about increased effectiveness in smoking cessation programs when NRT is provided without cost to the patient.

Of note, the report did confirm that NRT is cost effective in smoking cessation programmes as it results in a significantly higher rate of abstinence when compared with smoking cessation programmes without NRT.

The review also identified that side effects are common with NRT but are mostly minor. Studies reviewed in the report that sought to assess the risk of serious side effects, particularly cardiac side effects including chest pain and cardiac arrhythmias, reassuringly demonstrated no measurable increase in these events though the overall numbers are small and prescribers should continue to assess emerging evidence on this matter. Overall, the use of patches over the use of gum was shown to reduce side effects and side effects resolved on cessation of the NRT.

Overall, the horizon scanning report did not identify significant evidence in support of the practice of provision of free nicotine patches over payment for patches. Additional well-designed research studies are needed to determine if provision of NRT without cost as part of smoking cessation programs is effective in increasing smoking cessation rates.

For policy-makers and those instituting smoking cessation programs, current evidence does not specifically support providing NRT without cost to program participants. Nevertheless, there is also no clear evidence of any safety concerns if this approach is adopted.

It remains to be seen whether providing NRT free of cost as part of smoking cessation will assist in addressing the poor outcomes with smoking cessation in some community groups.

Introduction

The New Zealand Health Technology Assessment Unit, Department of Public Health and General Practice, Christchurch School of Medicine and Health Sciences, University of Otago, on behalf of the Medical Services Advisory Committee (MSAC) and the New Zealand Ministry of Health, has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play of the introduction and use of smoking cessation programmes for the distribution of free nicotine patches.

The serious health effects of smoking are indisputable. Smoking contributes to a wide range of morbidity and mortality in both Australia and New Zealand, and is responsible for 20% of the deaths in most Western countries. It shortens the life expectancy of addicts by an average of eight years and adds a huge burden to over-stretched health systems (Richards et al. 2003).

There are a number of randomised controlled trials supporting the effectiveness of nicotine replacement therapy (NRT). A Cochrane review of NRT efficacy concluded that all of the commercially available forms of NRT, including transdermal patches are effective as part of a strategy to promote smoking cessation. This report does not directly examine the effectiveness of nicotine patches as an intervention but considers whether the provision of nicotine patches, free of charge (rather than subsidised or at cost to the user) leads to significant improvements in quit rates and other behavioural outcomes for smokers.

Therapeutic Goods Administration (TGA) approval is not required for smoking cessation programs, however a number of brands of nicotine patches have TGA approval for use in Australia as aids to smoking cessation. Allied Master Chemists of Australia Ltd, Alphapharm Pty Ltd and Guardian Pharmacies Australia Pty Ltd all manufacture three strengths of nicotine patches: 17.5mg, 35mg and 52.5mg transdermal drug delivery sachets. In New Zealand, several brands of patch are available, one of which is subsidised by Pharmac (Pharmaceutical Management Agency) through the Quitline programme and the other is available for purchase over-the-counter. The patch strengths in New Zealand are the same as their Australian counterparts.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of smoking cessation programmes that include the distribution of free nicotine patches, their present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with smoking cessation programmes that include the distribution of free nicotine patches.

Description of the technology

Free Nicotine Patches

Nicotine replacement therapy (either as transdermal patches, gum or pharmaceutical options) is currently available in Australia and New Zealand as a user pays system through pharmacies. Quitlines which provide information, support and advice for smoking cessation are freely available in both countries.

Intended purpose

Historically, two substantial barriers to the wider use of nicotine patch therapy were the requirement for a physician's prescription and the cost of patches. The requirement for a prescription not only represented an obstacle but also added to the cost for any individual wanting to use nicotine patch therapy (Hays et al. 1999). Because of the desire to encourage more smokers to try and stop smoking and the demonstrated efficacy and tolerability of this intervention, nicotine patches were placed on the pharmacy only over-the-counter schedule when first classified as a new medicine in New Zealand in 1992. They were changed to general sales in August 2000. In Australia NRT became available over-the-counter from September 1997. The remaining issue of cost to the end user is being revisited with there being suggestion that removing this final barrier to access altogether may further increase the uptake of this effective quitting aid.

Clinical need and burden of disease

The deleterious effects of tobacco smoking have long been established. Current evidence has established a causal relationship between active smoking and 32 medical conditions, such as cancer (of the lung, mouth, pharynx, larynx, pancreas and kidney), chronic heart disease, stroke and chronic obstructive pulmonary disease. Sudden infant death syndrome, low birth weight of infants born to smoking mothers and asthma in exposed children, are well-documented effects of passive smoking (Ministerial Council on Drug Strategy 1999; Ministry of Health 2004). Furthermore, tobacco dependence is a chronic condition that may require repeated attempts to overcome. Approximately 70-80% of smokers make numerous attempts to quit and fail. Three to five per cent of smokers do succeed in quitting each year and the number of ex-smokers now outweighs the number of smokers in the Australian population (Australian Institute of Health and Welfare (AIHW) 2002). Quit Victoria research data from 2000 and 2001 indicated 40% and 39% of smokers respectively had attempted to quit in the previous year. In the 2000 survey, smokers were asked about their use of nicotine replacement therapy. Thirty-six per cent reported ever using patches and/or gum – with 27% reporting the use of patches. This is set in the context of at least 75% of smokers reporting ever attempting to quit (Letcher and Trotter 2003).

As the highest prevalence of smokers, particularly, heavy smokers, is in lower socioeconomic groups (higher unemployment, lower household income, lower

educational attainment), it follows that the most effective intervention (nicotine replacement therapy, NRT) would be more accessible if it were more affordable (The Cancer Council of South Australia 2002). Tauras (2003) estimated that a 10% price reduction of NRT products would increase their demand by up to 25%.

A systematic review of approximately 100 smoking cessation studies showed that in smokers who are motivated to quit, the cessation rate is 1.5 to 2 times higher in those using NRT compared to any other smoking cessation strategy (Silagy et al. 2006). Most of the data were based on studies investigating the effectiveness of NRT gum or patches. Other NRT methods, including nasal sprays, inhalers, and lozenges, or non-nicotine therapies, such as bupropion (Zyban), show similar increased rates of smoking cessation in controlled trials. All of these methods have been shown to be equally effective (Silagy et al. 2006). Moreover, the NRT is particularly effective in the more dependent heavy smokers who have a higher risk of developing smoking-related illness, find it more difficult to quit smoking and, therefore, are less able to quit smoking without assistance. In a placebo-controlled trial smoking cessation was two times more successful in heavy smokers who used nicotine patches compared to those who were given placebo patches, or who received counselling alone (Stapleton et al. 1995).

The proportion of regular smokers in Australia has fallen from 24.3% in 1991 to 17.4% in 2004, with 52.9% of the population having never smoked and 26.4% considered to be ex-smokers (Australian Institute of Health and Welfare (AIHW) 2005).

Smoking is the single, largest preventable cause of premature death and disease in Australia. The number of deaths attributable to tobacco in 1998 across Australia was 19,019. The majority of these deaths (78%) occur in the 65+ age bracket but 21% of deaths occur in the 35-64 age bracket. This equates to an estimate of 184,579 of person years lost. Hospital separations associated with the effects of tobacco have increased from 126,414 in 1995-96 to 142,525 in 1998, representing an increased burden on the health system. Cancer, ischaemic heart disease and chronic obstructive pulmonary disease as a result of smoking are responsible for 40, 21 and 20% of mortality, and 19, 26 and 20% of hospital separations, respectively (Miller & Draper 2001).

The 2002-03 health survey in New Zealand reported that the proportion of all adults who smoked daily was 22.9% (range 21.8-24.0%). Large differences existed between ethnic groups with Maori being more likely to currently smoke. Female Maori had higher rates of smoking (approximately 51%) compared to Maori males (42.5%). Current smoking prevalence was significantly higher in the "most deprived" quintile (approximately 33% and 37% for males and females, respectively). In addition, the New Zealand Health Survey estimated 6.7% (range 6.1-7.4) of adult non-smokers were exposed to passive smoke inside their homes. No data were available on the prevalence of passive smoking in children (Ministry of Health 2004).

It has been estimated that in 2002, 195 per 100,000 deaths in New Zealand were avoidable (potentially preventable through population or individual-based interventions). Approximately 80% of these avoidable deaths occur in the 45-74 year old age group and are dominated by chronic diseases such as ischaemic heart disease, diabetes and smoking related cancers (Ministry of Health 2005).

It is difficult to estimate the number of individuals who would wish to participate in a smoking cessation program, however during the 2004-2005 year, 11,586 individuals in

South Australia called the Quitline for help. The Health Omnibus estimates that in South Australia 78% of smokers have made an attempt to stop smoking at least once, 36% have attempted to stop smoking in the past 12 months and that 45% of smokers are seriously considering quitting in the next six months (Quit SA 2005). Based on a population of 1.5 million¹, approximately 0.7% of the population of South Australia attempted to stop smoking via the Quit line during 2004-2005. If this figure was extrapolated to the Australian population, then approximately 144,000² smokers may be motivated to cease smoking in one year.

Stage of development

The provision of free nicotine patches within smoking cessation programmes has been investigated by researchers, predominantly based in the US. Within Australia and New Zealand nicotine patches are already provided to smokers via quitline programmes. It has been proposed that provision of patches free of charge may provide an incentive for motivating people to make a quit attempt, would reduce the financial barriers to access and maximise the number of successful quit attempts. The primary users of free patches will be smokers wishing to quit who currently smoke in excess of 10 cigarettes per day.

Treatment Alternatives

Existing comparators

A wide variety of strategies and interventions to encourage smoking cessation have been developed including: individual or group counselling sessions (including Quitline, a smoking cessation help line that offers telephone support); specialist therapies such as acupuncture and hypnosis; pharmacotherapies, such as nicotine replacement therapy and bupropion (Zyban) (The Cancer Council of South Australia 2002). Bupropion has been associated with a number of adverse events including neuropsychiatric symptoms (tremors, agitation or confusion), insomnia, dry mouth and rash (Kolber et al. 2003). In a recent study by Paluck (2006), 205 adult smokers were enrolled in a smoking cessation study utilising bupropion. Although 21% of subjects abstained from smoking for 12 months, 70.4% experienced at least one adverse event and 29.6% reported stopping the drug due to adverse effects. In contrast, nicotine patches have been found to be an effective adjunct to simple advice and support given to motivated smokers in the setting of general practice or in smoking cessation centres with success rates much the same as those obtained with nicotine chewing gum. In some hospital patients with smoking related diseases transdermal nicotine seems to confer little benefit over advice and support alone (Campbell et al. 1995).

¹ Based on the current population level of 1,544,700 in South Australia. Australian Bureau of Statistics <http://www.abs.gov.au>

² Based on the current population level of Australia 20,647,116. Australian Bureau of Statistics <http://www.abs.gov.au>

A meta-analytic review compared over-the counter (OTC) nicotine replacement therapy (NRT) with placebo and prescription NRT. The authors concluded that OTC was efficacious and resulted in modest quit rates that were similar to those of prescription NRT. The review had a number of methodological weaknesses identified by the author (Hughes et al. 2006).

Clinical Outcomes

Effectiveness

There have been a range of different studies conducted on free nicotine patches with study designs ranging from randomised controlled trials (Level II evidence), comparative studies (Level III evidence) to cross-sectional, descriptive studies. Often within studies, free patches have been compared with free patches plus additional interventions so it is not possible to extract information about whether or not providing them free versus not free increases the effectiveness of smoking cessation programmes.

Level II Evidence

Eleven specific studies have used control groups and randomisation to intervention group. All studies that explicitly mentioned the use of free patches are profiled however there a variety of factors that limit the generalisability of many of these studies and make it difficult to make any conclusive statement about the effectiveness of free patches.

A pilot randomised controlled trial by Dey et al. (1999) provided a free supply of patches for about 12 weeks to those in the intervention group. Participants in the control group received a prescription for patches from their general practitioner. The authors suggest that their preliminary findings cast doubt on the idea that providing NRT is more effective than suggesting purchase but qualify this by saying that a more substantial study is needed. There were multiple methodological problems with this pilot including small sample size, differential response rates and extensive loss to follow-up.

Fiore et al. (2004) conducted an RCT in primary care that compared the provision of free patches with free patches plus a smoking cessation programme with patch, programme and counselling. This study, although well designed did not include any comparison condition, including usual care where patches were not provided free of charge.

Hays et al. (1999) ran two parallel 6-weeks trials, a placebo-controlled trial of 22mg, 24-hour free nicotine patch therapy and an open label placebo-controlled trial of the same therapy purchased by the subjects. Callers responding to advertisements for volunteers called a toll-free number with the call centre located separate from the study sites. Those who were eligible to participate in the research were then randomly assigned to one of the two trials, the open-label (payment) trial or the placebo-controlled (no payment trial). Smoking abstinence rates that were biochemically confirmed in the no payment trial were 16.8% versus 9.6% at week 6 and 8.7% versus 4.3% at week 24 for the active patch versus placebo groups, respectively. Smoking cessation rates in the open label-payment trial were

19% versus 9.6% and 10.8% versus 4.3% at weeks 6 and 24, respectively. For the no payment/placebo group versus the no payment active group the OR=2.2, 95% CI 1.1, 4.2 (p=.025) at week 24. Furthermore, for the no payment/placebo group versus the payment/active group the OR=2.7, 95% CI 1.4, 5.3 (p=.002). Being assigned to receive active patches (payment or no payment group) was associated with approximately double the rate of smoking abstinence at week 24. Self reported rates of abstinence (not biochemically confirmed) were about 2-4% higher across all groups but the difference remained significant.

The review by Silagy et al. (2006) notes that the Hays et al. study comparing the effectiveness of free and purchased patch found no significant difference in quit rates between the two conditions.

Pregnant women attending antenatal care received free patches (n=20) in a 12-week pilot RCT by Hotham et al. (2006). A control group of a further 20 women were offered counselling only. This small pilot study found there was low interest in participation and a high withdrawal rate. The authors suggest that patches may not be useful for this population but more research is needed.

Katz et al. (2004) conducted a trial of a comprehensive smoking cessation programme that included 8-weeks of free patches and/or counselling and was compared with usual care. The staff working in practices at control sites were provided with general information about the trial, and were aware that they were participating in a trial but were not told when they would receive training about the use of the intervention (all control sites received training at the end of the trial). Those at test sites were more likely to report being abstinent at 2-months (16.4% versus 5.8%). The odds of abstinence were higher at test sites compared to control sites at 2-months (adjusted OR=3.3, 95% CI 1.9, 5.6 p<0.001); and 6-months (15.4% versus 9.8%, adjusted OR=1.7, 95% CI 1.2, 2.6 p<0.009) follow-up assessments and the odds of continuous abstinence at both 2- and 6-months were higher. The authors concluded that the implementation of a guidelines based smoking cessation intervention by intake clinicians in primary care was associated with higher abstinence among smokers.

Solomon et al. (2005 and 2000) conducted two randomised controlled trials and compared free patches to free patches plus telephone support. No condition appears to have tested the effectiveness of patches that were not free although there was clearly some variation in the cost of filling a “free” prescription depending on health insurance status. For the first trial, the difference between groups in quit rate was significant at 10 days but not at 6-months. In the second trial, extended telephone support was offered for 6 weeks past the free supply of patches and there was a significant difference for both 7-day (p=0.035) and 30-day (p=0.002) abstinence. For 30-day abstinence the difference was sustained at both 3 and 6 months (p=0.052). This suggests that providing extended telephone support may have some additional effect over and above providing free patches alone but it is not clear from this trial whether providing free patches is more effective than usual care.

Sonderskov et al. (1997) compared free patches and placebo patches in a randomised controlled trial conducted with pharmacy customers. Smoking cessation was found to be significantly higher (p<.05) at 8 weeks with 28.7% (free patches) versus 18.3% (placebo) (Prevalence Proportion Ratio=1.56, 95% CI 1.01, 2.40), at 12 weeks with 18.4% (free

patches) versus 7.0% (placebo) (PPR=2.61, 95% CI 1.3, 5.23); and at 26 weeks, 11% (free patches) versus 4.2% (placebo) (PPR=2.61, 95% CI 1.04, 6.53).

An earlier trial reported in Russell et al. (1993) and Stapleton et al. (1995) showed that nicotine patch treatment that was free in the context of the trial doubled the rate of continuous abstinence up to 1-year (nicotine 9.6%, placebo 4.8%, $p < 0.01$). At 1-year the relative abstinence rate was 2.0 (95% CI 1.2, 3.3). Gradual reduction was no better at preventing relapse than abrupt withdrawal of patches after week 12.

Both these studies provide some evidence for the effectiveness of nicotine patches compared to placebo patches but again cannot distinguish any effect due to providing active patches from any effect due to their provision free of charge.

Stein et al. (2006) investigated the association between smoking and use of free nicotine patches in combination with other smoking cessation interventions. NRT use was inconsistent following an initial quit attempt among methadone maintained smokers. On the days where NRT was used, individuals were likely to smoke at reduced levels or not at all.

Finally, a trial by Wiggers et al. (2006) targeted cardiovascular outpatients. Patients in the experimental group were offered free patches plus a brief behavioural intervention. Those in the control group received usual care which implied they did not receive motivational counselling or self-help materials. Those who were adherent to treatment with patches were significantly more likely to have quit smoking (7-day abstinence) after 8 weeks than patients who were nonadherent (OR=2.48, 95% CI 1.28, 4.79). Half of the patients continued to smoke during NRT and only 38% of the patients were adherent to the 7-8 week time frame. The authors concluded that despite considerable attention to appliance instructions, access to free patches and additional behavioural support, adherence to NRT in these patients is relatively low. Both groups had access to the patches free of charge.

Level III Evidence

A controlled study by Nilsson et al. (1996) used pseudo-randomisation to allocate participants to free patches for up to 16-weeks and a support group examined the quit rates compared to a group receiving usual care. This study set in primary care reported an overall quit rate of 48% versus 91% who were still smoking in the control group at the 4-month follow-up. However the percentage of participants using patches rather than gum in this study was not clear.

A number of studies, mostly conducted in New York State, USA have examined the impact of providing free NRT on quit rates (Frieden et al. 2005; Miller et al. 2005).

Miller et al. (2005) examined the impact of providing a free 6-week course of NRT patches and two follow-up counselling calls to participants. Eligible³ smokers (n=34,090)

³ Eligible smokers defined as: ≥ 18 years of age; a resident of New York City; no medical contraindications to NRT patches; not using other NRT or bupropion; agreement to quit within one week of the screening call; smoked ≥ 10 cigarettes per day for >1 year; and agreed to be contacted for follow-up

who contacted a toll-free Quitline were sent a two-week supply each of generic 21mg, 14mg and 7mg nicotine patches, together with the usual literature to assist smokers to quit. Investigators attempted to make counselling phone calls, which included advice on patch usage, management of adverse reactions and encouragement to start or continue quitting to all NRT recipients at 3 and 14 weeks after the initial contact. At least one counselling call was received by 15,212 (45%) of the NRT recipients and 5,125 (15%) received two calls. Telemarketing staff were used to make the calls using a computer-assisted script. Promotional efforts and neighbourhood-specific media were used to target populations with the highest prevalence of heavy smokers.

At 6 months the smoking status of a randomly selected group of NRT recipients was assessed (n=1305) and compared to a group of eligible smokers (n=506) who did not receive NRT due to mailing errors. Adult's ≥ 65 years of age and foreign-born smokers were under-represented in the NRT recipients, and women were more likely to participate. No information was provided in the published report regarding safety issues.

NRT recipients who provided data on quit attempts were more likely to attempt to quit smoking (87%, 1135/1305, 95% CI 86%, 89% $p < 0.0001$) versus the comparison group respondents (53%, 84/159), an odds ratio of 6.0 (95% CI 4.2, 8.6). Successful quitters were more likely to report using all the patches (51%, $p < 0.0001$) than those still smoking at 6 months (24%). Successful quitting was reported in 33% (435/1305) of NRT recipients and 6% (10/159) of the comparison group respondents ($p < 0.0001$). Successful quits were associated with NRT receipt after adjustment for demographics and smoking status (adjusted odds ratio 8.8, 95% CI 4.4, 17.8). If all follow-up survey non-respondents are assumed to continue to smoke then 20% of NRT recipients and 2% of comparison group participants quit smoking (attributable quit rate of 18%).

NRT recipients who received counselling calls were more likely to stop (38%) than those who did not (29%) with an adjusted odds ratio of 1.5, 95% CI 1.1, 1.9. However counselling calls were only effective in those who smoked < 20 cigarettes per day. The quit rate in those who smoked < 1 pack per day at enrolment who received a counselling call was 50 per cent versus 27 per cent for those that received no call ($p < 0.001$).

The additional cost of the programme including the purchase of NRT, Quitline and counselling staff and shipping was estimated to be US\$2.8 million. Therefore the cost per successful quit was estimated to be US\$266 using the 33% quit rate reported by NRT recipient respondents (alternatively, US\$464 per successful quit using the 18% attributable quit rate). Given that these data were not derived from an RCT they may overestimate effectiveness.

A second level III.2 study by Katz and colleagues (2002) was run within the primary care (family practice) setting. In this study, investigators were seeking to test the effectiveness of a clinic-based strategy for implementing Smoking Cessation Guidelines (Agency for Healthcare Research and Quality). This non-randomised controlled before-and-after trial (pilot study) included free nicotine replacement therapy and telephone counselling of smokers willing to make a quit attempt within the participating practice. Patterns of usual care were observed concurrently at four control family practice clinics. Overall exit interviews were obtained from 651 consecutive adult smokers who presented for routine, non-emergency care. Abstinence (7-day point prevalence) was determined by telephone

interview during the 6-month follow-up. Significantly more intervention versus baseline patients at the test site reported abstinence at the 2-month follow-up (21% versus 4%, $p=0.0004$), and more patients tended to be abstinent at 6-month follow-up (21 versus 11%, $p=0.08$). No significant differences in 2- or 6-month quit rates between intervention and baseline patients were observed at the control sites.

At least nine other non-randomised, comparative studies, with before-and-after study designs were identified by the search strategy.

Bauer et al. (2006) compared the quit rates in smokers who redeemed a voucher for a free 2-week supply of nicotine gum or patches obtained by calling the Quitline (level III-3 intervention evidence). A follow-up survey was conducted 4-6 months after this initial contact. A historical comparison group of 515 smokers who had called the Quitline prior to the free NRT voucher also completed a follow-up survey (Bauer et al. 2006). Of the enrolled smokers, 75% redeemed their vouchers for patches and 25% for gum. Quit rates for smokers who used patches and gum were 30 and 26 per cent, respectively. The quit rate in the historical comparison group was 12 per cent. The adjusted relative risk for quitting was 1.77 (95% CI 1.17, 2.68) for those who received a free NRT voucher compared with those that did not control for age, gender, race, type of health insurance, and use of other quit methods. Of the smokers who completed the follow-up survey and used the patch or gum at least once, 7% (35/513) stated they had discontinued therapy due to side effects.

Hawk (2006) compared the quit rates in smokers who entered a “quit and win contest” (level III-3 intervention evidence). The contest offered daily smokers the chance to win prizes ($n=849$), including a grand prize of US\$1,000, if they stopped smoking for a month, versus smokers screened via the Quitline who received a voucher for a free 2-week supply of nicotine gum or patch ($n=690$). A smaller group of smokers participated in both programmes ($n=230$). After a median length of 5.5 months (range 4-7 months), participants in the quit and win (38%), NRT voucher (44%) and combination group (97%), respectively were followed up. Abstinence rates of 29%, 26% and 27% respectively were reported for each programme and a longer follow-up period was associated with reduced abstinence. Assuming that non-respondents in the survey continued to smoke, the reported quit rates were between 15-17%. Smokers who entered the quit & win competition tended to be younger than those who signed up for free NRT.

A summary of four NRT giveaway intervention programmes (level III-3 intervention evidence) in New York State utilising the Smokers’ Quitline reported 21-33% of survey respondents were not smoking at the time of the follow-up survey compared with 12% of Quitline callers who received counselling support and a free cessation guide but no free NRT (Cummings et al. 2006a; Cummings et al. 2006b). All participants received a stop smoking guide and an information sheet on local stop smoking programmes and all participants that could be contacted received a telephone call counselling them about quitting smoking. Quit rates were reported at the 4-month follow-up telephone interview.

Approximately 30% of participants reported ≥ 2 side effects whilst using NRT. Side effects were reported in 27-46% of the 1-week or 2-week programme whilst 52% reported side effects in the 6-week programme. Medication was discontinued in 3-9% of

participants because of side effects. Among those with side effects 32-44% reported sleep disturbance, 7-17% reported skin rashes and 4-15% had heart palpitations.

Huang et al. (2005) recruited a small sample of ten adult smokers to a smoking cessation support group. This before-and-after study set in the community provided free nicotine patches for the 3-month duration of the programme. Seven of the ten participants used them. At 9-month follow-up 50% were abstinent and 30% had decreased their consumption 30%. Abstinence was validated by measuring carbon monoxide in the breath.

Only one study provided long-term follow-up data (18 months), assessing the addition of free NRT to a group behavioural cessation programme (level III-3 intervention evidence) (Alberg et al. 2004). The group behavioural cessation programme consisted of two sessions per week for four weeks covering topics such as tips for quitting, fears of quitting, recovery symptoms, positive self-talk and how to develop a quit plan (n=601). Programme participants who enrolled later (n=311) received a free 6-week supply of 14mg or 21mg 24-hour patches. Patches were distributed at weekly intervals for 3 weeks and then the remaining amount was supplied. Quit rates were significantly higher in patients that received free NRT at the end of the programme (66%) versus those that participated in the programme alone (38%) (risk difference 27%, 95% CI [21%, 34%]). Adjustment for potential confounding variables (gender, age, education, years smoked, cigarettes/ day, pack years, and sessions attended) reduced the risk difference to 17%, 95% CI [11%, 22%]. However, the quit rates were not sustained during the 18-month follow-up period. Quit rates were lower (6.7%) in the programme plus free NRT participants compared to 14.3 per cent in smokers who participated in the programme alone. No information was provided in the published report regarding safety issues.

An Australian study by Ivers et al. (2003) assessed the use of free nicotine patches by indigenous people when offered a brief intervention for smoking cessation in primary care. Pre and post test measures of use were utilised. Forty smokers self-selected to receive the patches (n=71 chose the brief intervention) for up to 10-weeks. Quit rates at 6-months were 15% for the patches and 1% for the brief intervention. Reduced use was noted in 76% of the patches group compared with 51% of the brief intervention group but only a small percent of the outcomes were carbon monoxide validated. Overall no participant completed a full course of free patches and cessation rates in this group were lower than those for other populations.

A prospective, open-label study (Jolicoeur et al. 2000; Jolicoeur et al. 2003) evaluated the impact of free nicotine patches with minimal support for smoking cessation. All participants (n=223) received approximately 6-weeks (42 patches) of free patches plus a self-help guide. The overall quit rate defined as having not smoked a cigarette in 7-days was 21% at 6-weeks and 22% at 6 months. The 7-day continuous abstinence at 6-weeks and 6-months was 12%.

Der et al. (2001) describe a clinic-based, medical-student run smoking intervention clinic that offered free patches for 12 or more weeks as part of their programme. NRT patches were used by 63% of the sample. Of the 88 participants, 36% (95% CI 22%, 52%) were reported as abstinent six months after the initial visit. If the 44 patients not interviewed who were lost to follow-up were assumed to be smoking at six months after their initial

visit, the 6-month abstinent rate was lower at 18%, 95% CI 11%, 28%. This smoking intervention programme yielded smoking abstinence rates comparable to other treatment programmes but did not separate out the effect of the free patches.

Wadland et al. (1999) conducted a study with n=487 participants comparing free NRT plus practice-based counselling with free NRT plus telephone counselling. Both a practice-based and community-based approach to the delivery of counselling was adopted and free patches were available in both settings for the 10-week intervention period. At 6-months, quit rates (7-day smoke free status) were 35% in the practice-based group and 36% in the community-based group. An increased quit rate was noted for individuals attending four or more counseling sessions. Sixty-two percent of the participants obtained NRT (patch or gum) with 95% of the sample opting for patches. This study did not include a no-NRT condition so it is not possible to determine the effect of the free patches.

Safety

Side effects usually reported with nicotine gum, including hiccoughs, gastrointestinal disturbances, jaw pain, and orodental problems, are not seen with the transdermal patch. The only side effect which appears to interfere with the use of the patch is skin sensitivity and irritation; this may affect up to 54% of patch users, but is usually mild and rarely leads to withdrawal of patch use (Fiore et al. 1992).

The review on NRT for smoking cessation by Silagy et al. (2006) noted there have been some concerns about the safety of NRT in smokers with cardiac disease. A trial of nicotine patch which recruited smokers aged over 45 with at least one diagnosis of cardiovascular disease found no evidence that serious adverse events were more common in smokers in the nicotine patch group (Joseph et al. 1996). Events related to cardiovascular disease such as an increase in angina severity occurred in approximately 16% of patients, but did not differ according to whether or not patients were receiving NRT. A review of inpatients with cardiovascular disease found no evidence of an increased risk of cardiac events (Joseph and Fu 2003).

Khoury et al. (1996) examined the cardiovascular effects and safety of transdermal nicotine patches in 50 healthy smokers using repeated 48 hour ambulatory electrocardiographic monitoring as a part of a smoking cessation program. Following baseline measurements, subjects were randomized to active (n = 25) or placebo (n = 25) treatment groups for a period of 2 weeks. Twenty-two patients in each group completed the trial. There were no significant side effects in either the placebo or the active treatment groups. Results of the trial indicated that nicotine delivered by transdermal system appears to be free of cardiac adverse effects in healthy volunteers, at least in the short-term.

No additional safety considerations are associated with the use of free patches compared with patches at cost to the user, except perhaps that some smokers less motivated to quit may continue to smoke while using patches.

Cost Analysis

Due to the lack of evidence based data for cost effectiveness, a simple cost analysis is appropriate.

Alphapharm Pty Ltd provides 3 doses (7mg, 14mg and 21mg) of nicotine patches (QuitX) in packs of seven (one weeks supply), ranging in price from \$A17.64 - \$A21.30 (cost price available to chemists)⁴. A six week cessation program would therefore cost approximately \$A106 - \$A128 per individual (wholesale). Quitline provides patches over-the-counter for \$A30-\$A45 per week, depending on brand and strength of patch. Therefore a 6 week cessation program would cost approximately \$A180-\$A270 (retail)⁵

In New Zealand: Nicoderm/Nicobate patches packs of seven range in price from \$NZD23.00-\$NZ28.33 (based on wholesale pharmacy price). A six week cessation program would therefore cost approximately \$NZ138 - \$NZ170 per individual.

Several authors have examined the cost effectiveness of nicotine replacement therapy programmes, with two recent studies directly addressing the issue of free NRT.

Cummings et al. (2006a) measured the cost-effectiveness of each programme in terms of smoker enrolment and quit rates, relative to the cost associated with offering NRT and advertising the programme. Programme costs included those associated with marketing, purchasing, and mailing out the free NRT, and the costs of registering and counselling smokers when they called the Quitline.

The cost per extra quit attributable to NRT for the different programmes was \$US274 (2-week voucher), \$US306 (by mail 1-week) and \$US347 (by mail 2-week and 6-week). A quit rate figure of 12% from their July 2001 follow-up survey of Quitline callers was used as an estimate of the number of smokers who would quit in the absence of the NRT giveaway.

Ong and Glantz. (2005) conducted a cost-effectiveness comparison between the provision of free nicotine replacement therapy and implementing smoke-free workplaces. The cost of a quit attempt was calculated as the product cost multiplied by the recommended duration of therapy (8 weeks for patches). With a 2:5 ratio of gum:patch use the average cost of a quit attempt with NRT was \$US185.34. This estimate did not include the costs of administering a free NRT programme, such as advertising, coordination, subsidies or any counselling or support through a telephone quitline. After one year they estimated that a NRT programme generated 18500 quitters at a cost of about \$US7020 per quitter (\$US4440 per quality-adjusted life year/QALY) using 2002 average wholesale prices for the most inexpensive NRTs. Smoke-free workplace policies generated 10,400 quitters at a cost of \$US799 per quitter (\$US506 per QALY). The authors suggest smoke-free

⁴ Personal communication May 1st Alphapharm Pty Ltd

⁵ QuitSA, http://www.quitsa.org.au/asp/contact_us.aspx

workplace policies are about nine times more cost-effective than free NRT programmes (Ong and Glantz 2005).

These results on the cost effectiveness of providing NRT free of charge should be considered in light of the relative paucity of randomised controlled studies that directly compare free patches with purchased patches.

In a randomised placebo-controlled trial, Stapleton et al. (1999) estimated the cost-effectiveness for the National Health Service in Britain if general practitioners (GP) were able to prescribe nicotine patches for 12-weeks (Stapleton et al. 1999). The health benefits in number of life years saved by stopping smoking at various stages of life were calculated, comparing brief counselling by the GP in conjunction with the prescription of nicotine patches, to brief counselling alone (see **Table 1**).

Table 1. Cost-effectiveness of GP counselling plus nicotine patches, incremental to brief counselling by GP alone

Age when treated	Extra cost per patient treated (£)	Extra life years saved per patient treated	Incremental cost-effectiveness ratio (£)
Under 35 years	34.15	0.086	397.95
35-44 years	34.15	0.099	344.68
45-54 years	34.15	0.079	432.32
55-65 years	43.08	0.055	785.43

After Stapleton et al. (1999)

The incremental cost per life year saved ranged from £398 per person under 35 years, to £785 per person aged 55-65 years. The relatively low cost per life year saved was viewed by the authors as a small investment for a potential future that will require less expenditure in smoking-related illnesses.

There is uncertainty about the total potential cost of offering free nicotine patches due to the uncertainty involved in estimating the number of quit attempts that would make use of free patches. If it is assumed that 40% of current smokers attempt to quit in any given year, that 27% of these use nicotine patches, the prevalence of current smoking is 18% of the population (based on a population of 20M in Australia and 4M in New Zealand) and that the wholesale prices for nicotine patches represent the total cost of such a service, then the total cost of the programme in Australia for one year approximates \$A41M to \$A50M. If similar proportions are assumed in New Zealand, the total one year cost would approximate \$NZ11M - \$NZ13M. Note, however, that there is large uncertainty in determining the proportion that would choose to use free nicotine replacement patches when attempting to quit smoking. Infrastructural costs are not included in these cost estimates.

Informed Consent

Patients participating in RCT intervention studies of free NRT profiled were required to provide informed consent and generally reported this. Publications from other observational studies (Level III.2 and III.3) did not always report on this issue.

Access Issues

There is a clear association between low socio-economic status and a high prevalence of smoking. Individuals in lower socio-economic groups may be less likely to access nicotine replacement therapy due to the perceived initial expense. Although some investigators have looked at specifically providing free patches to low-income groups logistical problems were encountered in engaging health providers that lacked staffing to implement or coordinate smoking cessation programmes (Lickteig et al. 1993). Subsequent studies conducted in the US appear to have overcome these initial difficulties. As long as users have access to a pharmacy that can dispense or supply the patches, free patches should be obtainable or a voucher for free patches redeemed in rural or non-metropolitan areas.

A reduction in the cost of NRT has increased use and cessation in some studies, but not others (Miller and Wood 2002; Miller et al. 2005). This conflicting evidence suggests that other factors, such as convenience should also be addressed. Some free NRT distribution efforts could still pose logistical barriers if smokers are asked to redeem vouchers, travel to a pick-up location, purchase additional medication, or receive counselling to complete a course of treatment (Miller et al. 2005).

Training and Accreditation

Training

There are no new training requirements to provide free patches beyond what would already be required to provide patches subsidised (through Quitlines), prescribed or at full retail cost to the user. Some general practitioners and their practice nurses might require training to offer adjunctive therapies or refer to community-based programmes where free patches are offered in the context of a comprehensive smoking cessation programme.

Clinical Guidelines

A large number of guidelines on smoking cessation exist internationally. In Australia, the Joanna Briggs Joanna Briggs Institute for Evidence Based Nursing and Midwifery provides a “Best Practice Information Sheet” at:

http://www.joannabriggs.edu.au/best_practice/BPISsmok.php (2001). A New Zealand-based guideline can be found at:

http://www.nzgg.org.nz/guidelines/0025/Smoking_Cessation_full.pdf (2002)

Many other entities have published guidelines on smoking cessation and the effectiveness of nicotine replacement therapy using transdermal patches.⁶

Current guidelines on smoking cessation programmes should be adequate to incorporate any policy change. Guidelines and some associated information or fact sheets would need to have details on cost or subsidies amended if patches were provided free of charge.

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology. Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

⁶ Other websites with relevant guidelines include but are not limited to <http://www.ash.org.uk/html/cessation/Smoking%20reduction/NARS051014.pdf> on nicotine replacement (2005), British Thoracic Society at <http://thorax.bmjournals.com/cgi/reprint/55/12/987.pdf>, the US guidelines clearing house <http://www.guidelines.gov>.

A Horizon Scanning Report maintains a predictive or speculative focus, often based on low-level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology. In this instance although randomised controlled trials have been conducted looking at the effectiveness of free nicotine patches, mostly findings have not been reported for a comparison group using patches for which some payment was required. One exception to this was the parallel trials conducted by Hays (1999), the authors of these trials comment that a true simulation of an over-the-counter environment requires that subjects pay for their medication. This causes a dilemma for investigators who wish to perform a placebo-controlled trial in an over-the-counter environment, because it would be unethical to ask volunteer subjects to pay for the placebo. These authors ran an open-label pay trial alongside their placebo-controlled trial to address this issue.

Several studies were focused on specific populations (eg. pregnant women, methadone maintained smokers, cardiovascular outpatients) or excluded specific populations (eg. pregnant or breastfeeding women, people with depression) so they may lack generalisability.

Studies used different thresholds (number of cigarettes smoked daily) for determining whether patients had access to patches. Generally, heavy smokers were classed as those smoking 10 or more cigarettes per day but this was not without exception.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of free transdermal nicotine patches, its present and potential use in the Australian and New Zealand public health system, and future implications for the use of this technology.

Search Strategy used for the Report

The medical literature in **Table 1** was searched up until 30 July 2006 utilising the search terms outlined in **Table 2** to identify relevant studies and reviews. In addition, major international health assessment databases were searched.

Table 2. Literature sources utilised in assessment

Source	Location
Cinahl	Ovid
Cochrane Library –Cochrane Database of Systematic Review and the Cochrane Central Register of Controlled Trials (CENTRAL	Wiley Interscience
Current Contents	Thomson ISI
Embase	Ovid
Medline	Ovid
PsychInfo	Ovid
Web of Science	Thomson ISI
Internet	
Australian Health & Medical Research Council	http://www.nhmrc.gov.au
Centre for Reviews & Dissemination Databases: Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, NHS Economic Evaluation Database	http://www.york.ac.uk/inst/crd/crddatabases.htm
ClinicalTrials.gov	http://www.clinicaltrials.gov
Current Controlled Trials metaRegister	http://controlled-trials.com/
Guidelines International Network Health Topics collection	http://www.g-i-n.org
National Institute for Clinical Excellence (NICE)	http://www.nice.nhs.uk
New Zealand Guidelines Group	http://www.nzgg.org.nz
Trip database	http://www.tripdatabase.com
US Guidelines Clearing House	http://www.guidelines.gov
UK Guidelines Finder Library	http://www.library.nhs.uk/guidelinesfinder/

Table 3. Search terms utilised

Search terms
MeSH Smoking cessation
Text words ((free or giveaway or subsid\$) adj2 nicotine adj (replacement or patch\$)).mp. , ((free or giveaway or subsid\$) adj2 NRT
Limits English

Availability and Level of Evidence

No restriction was placed on the level of evidence sought. However only level I, II and III studies are summarised in the section on clinical effectiveness. Although a number of RCTS on free patches were located from the search strategy (n=11), many were subject to a number of significant design limitations including small sample size and a lack of appropriate comparators. Therefore Level III intervention evidence that more directly addressed the topic was also included (n=12). One level III.1 study, two level III.2 studies

and nine Level III.3 studies were identified. Level IV studies are profiled for background only. All studies are briefly profiled in Appendix B.

Sources of Further Information

A large number of trials (>20) that include nicotine replacement therapy with patches are listed on current trial registers. None of these specifically mention free patches as the active intervention within the title or short description of the trial. It is possible, if not likely that within these trials nicotine patches are being provided free of charge to participants.

Impact Summary

The health hazards of smoking are significant and well established. The effectiveness of HRT as an aid to smoking cessation has been thoroughly investigated. The evidence indicates unequivocally that NRT as an aid to smoking cessation is more effective than placebo. Published economic studies of smoking cessation have adopted different methods and assumptions for estimating effectiveness and cost but most results indicate that adding NRT to usual care is cost-effective with a relatively low incremental cost per quitter (Woolacott et al. 2002). Free provision of NRT may encourage more cessation activity and therefore show corresponding benefits for public health but the effectiveness and cost effectiveness of this approach have yet to be finally determined.

Conclusions

All forms of NRT can help people quit smoking, almost doubling long-term success rates. Silagy et al. (2006) highlights the fact that it is not clear whether any one form of NRT is better than another. Patches appear to be a well tolerated aid for some but not all groups of smokers wishing to quit.

A total of 11 randomised controlled trials (Level II intervention evidence) and 12 (Level III intervention evidence) were identified as addressing the issue of free provision of nicotine replacement based on the criteria that the abstract or title of the article explicitly mentioned this.

Overall, despite the number of studies the evidence from randomised controlled trials is equivocal. While NRT provided free is more effective than placebo, it is not clear whether the observed effect is over and above what it would be if the NRT was provided at cost to the user. Study design and response rate issues limit the conclusions that can be made from the only trial that directly compared a group receiving a free supply of patches to a group receiving a prescription (Dey et al. 1999).

Findings from Level III studies that have utilised control groups are more positive. A range of studies have considered the impact of providing free patches with the New York study investigators reporting successful quits to be associated with the receipt of free NRT. Short-term abstinence (2-months) is higher with longer-term abstinence (6-months) showing a similar, albeit weaker trend.

Before-and-after studies vary and generally but not exclusively favour free NRT, in the short-term. One study suggested that any increase in quit rates are not sustained. Offering free patches may initially stimulate more smokers to enrol in a programme and the adjunctive use of patches may enhance the impact of group counselling in smoking cessation however there have been some concerns that there may also be potential for a more rapid rate of reversion. This is as yet unproven. Moreover, relatively few studies provided detailed information on safety issues.

In conclusion, the provision of free nicotine patches to smokers appears to be more effective for smoking cessation than usual care counselling alone in the short-term. Long-term follow-up data were reported by only one study, which indicated that cessation rates were greater in smokers who received counselling alone compared to smokers who received free NRT.

There is insufficient evidence to determine whether providing patches free is any more effective than providing potential quitters with a prescription, subsidy or voucher to purchase patches at a reduced price.

Future provision of free NRT should preferably be piloted within the context of a randomised controlled trial. Data on its effectiveness in increasing the uptake of NRT as part of smoking quit attempts, given its proven effectiveness in increasing quit success rates, could then be obtained and compared with partly subsidised or full-cost NRT.

Appendix A: Levels of Evidence

Table 4 Designation of levels of evidence according to type of research question

Level	Intervention [§]	Diagnosis ^{**}	Prognosis	Aetiology ^{†††}	Screening
I*	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ^{§§} among consecutive patients with a defined clinical presentation ^{††}	A prospective cohort study ^{***}	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ^{§§} among non-consecutive patients with a defined clinical presentation ^{††}	All or none ^{§§§}	All or none ^{§§§}	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial [†] Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study

Table 4 Designation of levels of evidence according to type of research question (continued)

Level	Intervention §	Diagnosis **	Prognosis	Aetiology †††	Screening
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study † Interrupted time series without a parallel control group	Diagnostic case-control study ††	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ††	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Table notes

* A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

§ Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

† This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C).

‡ Comparing single arm studies ie. case series from two studies.

** The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies*. Available at: www.msac.gov.au.

§§ The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology*, 2003, 3: 25.

†† Well-designed population based case-control studies (eg population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. These types of studies should be considered as Level II evidence. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

†† Studies of diagnostic yield provide the yield of diseased patients, as determined by an index test, without confirmation of accuracy by a reference standard. These may be the only alternative when there is no reliable reference standard.

*** At study inception the cohort is either non-diseased or all at the same stage of the disease.

§§§ All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

††† If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence etc.

Hierarchies adapted and modified from: NHMRC 1999; (Bandolier editorial 1999; Lijmer et al. 1999; Phillips et al. 2001)

Appendix B: Profiles of studies

Table 5. Related systematic reviews and meta-analyses⁷ (Level I intervention evidence)

Author, Country	Study Design Intervention (n, duration of free supply), Setting	Results	Comment
(Hey and Perera 2006)	Systematic review and meta-analysis of RCTs and controlled studies with baseline and post-intervention measures. n=15 studies met inclusion criteria.	Authors concluded that incentives and competitions do not appear to enhance long-term cessation rates, with early success tending to dissipate when rewards are no longer offered.	Only three studies used NRT and only one of these used patches (Shoptaw et al. 2002). This review did not specifically look at free provision as an incentive.
(Hughes et al. 2006)	Systematic review and meta-analysis of controlled trials of over-the-counter (OTC) NRT versus placebo or OTC NRT versus prescription NRT for smoking cessation. n=4 trials.	Authors concluded that OTC NRT is pharmacologically efficacious and produces modest quit rates similar to that in real world prescription practice.	This review notes that for ethical reasons OTC NRT trials that include placebo arms provide medication free of charge. Provision of free medication may increase quit rates compared to requiring subjects to pay for NRT, thus the OTC NRT versus OTC placebo studies may overestimate real world quit rates.
(Silagy et al. 2006)	Systematic review and meta-analysis of RCTs comparing NRT to placebo or no treatment, or where different doses of NRT were compared. n=123 trials; 103 contributed to primary comparisons.	Authors concluded all forms of NRT are effective as part of a strategy to promote smoking cessation. The odds of quitting are increased 1.5-2 fold regardless of setting. The effectiveness appears to be independent of the intensity of providing additional support to the smoker. Provision of more intense levels of support, although beneficial in terms of facilitating the likelihood of quitting, is not essential to the success of NRT.	37 of the trials considered patches. No explicit statement in this review about whether patches were provided free or not within the context of the trials reviewed. One trial that compared free and purchased patches was identified (Hays et al. 1999).

⁷ None of the three systematic reviews or meta analyses reported here were restricted to RCTs on nicotine patch therapy (inclusion criteria usually covered different types of NRT and/or a variety of hypotheses) nor did they focus specifically on free provision versus usual care.

Table 6. Randomised Controlled Trials (Level II intervention evidence)

Author, Country	Study Design Intervention (n, duration of free supply), Setting	Results	Comment
(Dey et al. 1999), UK	Pilot RCT free patches versus prescribed patches n=64 (exp) n=58 (control) Approx 12 weeks General practice	Self-reported smoking status at 14 weeks 24% free group compared to 17.9% in purchase group. Preliminary findings cast doubt on the idea that providing NRT is more effective than suggesting purchase but a more substantial study is needed.	There are multiple methodological problems with this pilot including small sample size, differential response rates and extensive loss by the final follow-up. Salivary cotinine for validating abstinence was available in a very small number of participants.
(Fiore et al. 2004), USA	RCT free patches versus free patches plus counselling in one arm and self-selection arm also n=961 (free patch arm) n=908 (self selection arm) 8-weeks Primary care	Intent-to-treat CO confirmed point (and continuous prevalence rates at 6mths) Patch only (12%) Patch plus CQ (13.7%) Patch plus CQ plus counselling (16.1%) Psychosocial treatment components did not significantly increase abstinence rates.	Used Committed Quitters (CQ) Program. 7-day point-prevalence and continuous abstinence, follow-up at 1 year also. Did not assess effectiveness compared to patches that were not provided free.
(Hays et al. 1999 ⁸), USA	RCT Open trial (2 nd comparison group) n=958 6-weeks Over-the-counter (retail)	Smoking cessation rates in the placebo controlled trial were 16.8% versus 9.6% at week 6 and 8.7% versus 4.3% at week 24 for the active patch and placebo groups, respectively. Smoking cessation rates in the placebo controlled trial were 19% versus 9.6% and 10.8% versus 4.3% at weeks 6 and 24 respectively.	To determine the efficacy and safety of the nicotine patch for smoking cessation in an over-the-counter environment. A slight increase in cardiovascular events was noted only in the open-label pay group in comparison with the placebo group.

⁸ This study involved a double-blind placebo-controlled trial of patches (level II intervention evidence) and a concurrent open label trial of active patch therapy (comparison group) in which participants paid for the patches (level IV intervention evidence).

Table 6. Randomised Controlled Trials (Level II intervention evidence) (continued)

Author, Country	Study Design Intervention (n, duration of free supply), Setting	Results	Comment
(Hotham et al. 2006), Australia	Pilot RCT free patches versus no patches 12-weeks Hospital	Quit rates Cessation in 15% patch group versus 0% control	Pregnant women attending antenatal care High withdrawal rate from women Patches may not be highly useful for pregnant women
(Katz et al. 2004), USA	RCT Free patches and/or brief counselling versus usual care n=8 practices n=1008 (exp) n=1155 (control) 8-weeks Primary care (family practice)	Those at test sites were more likely than those at control sites to report being abstinent at 2-months (16.4% versus 5.8%), adj OR=3.3, 95% CI 1.9,5.6 p<.001; and 6-months (15.4% versus 9.8%), adj OR=1.7, 95% CI 1.2,2.6 p<.009 follow-up assessments and continuous abstinence at both assessments (10.9% versus 3.8%), adj OR=3.4, 95% CI 1.8,6.3 p<.001.	Randomisation by practice Hierarchical modelling used to account for clustering. Cannot extract the specific effect of free patches from this trial.
(Solomon et al. 2005), USA	RCT Free patches plus telephone support (n=179) versus free patches (n=159, control) 8-10 weeks Community	For experimental group 7-day (48%) and 30-day (42.7%) point prevalence abstinence compared to the control group (36.5%) and (26.4%) respectively. There was a significant difference between groups for both 7-day (p=.035) and 30-day (p=.002) abstinence. For 30-day abstinence at both 3 and 6 months 28.7% versus 19.5% (p=.052).	As per Solomon (2000) but extended telephone support for 6 weeks past free supply of patches.

Table 6. Randomised Controlled Trials (Level II intervention evidence) (continued)

Author, Country	Study Design Intervention (n, duration of free supply), Setting	Results	Comment
(Solomon et al. 2000), USA	RCT Free patches plus telephone support (n=106) versus free patches (n=108, control) 8-10 weeks Community	Reported abstinence all smokers, for patches plus support (42%) versus patches only (28%). At the 3-month follow-up: the experimental group quit rate at 10-day and 3-months (32%) compared to the control group (19%), (p=.02). At the 6-month follow-up for experimental group quit rates at 3- and 6-months were (20%) compared to 15% in the control group (ns).	Specifically targeted low-income women. Patches were free in both groups so the focus of this study is primarily on the added value of using telephone support with free NRT. There was some variation in the cost of filling a free prescription depending on health insurance status. Prescriptions for patches and/or vouchers were sent by mail.
(Sonderskov et al. 1997) Denmark	RCT Free patches (n=255) versus placebo (n=267) patches 12-weeks Community (via pharmacies)	Smoking cessation after 12 weeks 18.4% (patches) versus 7.0% (placebo), PPR=2.61, 95% CI 1.3,5.23; at 12 weeks 11% versus 4.2%, PPR=2.61, 95% CI 1.04,6.53.	The primary outcome measure was the prevalence proportion ratio (PPR). Only 21mg/day patches were effective and a placebo effect was observed at each time of contact in the trial.
(Stapleton et al. 1995) UK	RCT Free patches (n=800) versus placebo (n=400) 12-weeks General practice	Nicotine patch treatment doubled the rate of continuous abstinence up to 1-year (nicotine 9.6%, placebo 4.8%, p<.01). At 1-year relative abstinence rate 2.0 95% CI 1.2, 3.3. Gradual reduction was no better at preventing relapse than abrupt withdrawal of patches after week 12.	99% of subjects that achieved abstinence in the study quit during the first week of cessation. A variety of people were excluded from the trial, including those with symptoms of depression.

Table 6. Randomised Controlled Trials (Level II intervention evidence) (continued)

Author, Country	Study Design Intervention (n, duration of free supply), Setting	Results	Comment
(Stein et al. 2006) USA	RCT Free patches versus patches plus brief motivational therapy or brief advice n=309 (total sample) 8-12 weeks Clinic (methadone)	The odds of smoking (7- day) abstinence were higher on the days when NRT was used (day 1- 90) OR=7.05, 95% CI 5.42, 9.14; (day 91-180) OR= 7.16, 95% CI 3.86, 13.25. Patch use was inconsistent but when used, individuals were likely to smoke at reduced levels or not at all.	Specific programme delivered in methadone treatment centres.
(Wiggers et al. 2006) The Netherlands	RCT Free patches (n=174) plus brief behavioural intervention versus usual care 8-weeks Clinic (cardiovascular outpatients)	Patients who were adherent to NRT treatment were significantly more likely to have quit smoking (7- day abstinence) after 8 weeks than patients who were nonadherent (OR=2.48, 95% CI 1.28, 4.79).	Motivation to quit did not influence adherence to NRT. NRT was provided to outpatients who smoked > 5 cigarettes per day.

Table 7. Controlled or Comparative Studies (Level III intervention evidence)

Author, Country	Study Design Intervention (n, duration of free supply), Setting	Results	Comment
Level III.1			
(Nilsson et al. 1996), weden	Controlled study Free patches and support group versus usual care Up to 16-weeks Primary care	Overall quit rate was 48% versus 91% still smoking in control group at 4-month follow-up.	Chewing gum was also offered alone or in combination. Percent using patches in study not clear. Pseudo-randomisation.
Level III.2			
(Katz et al. 2002), USA	Nonrandomised controlled trial (III.2) Free patches and/or brief counselling (n=666) versus usual care (n=346) 8-weeks Primary care (family practice)	Quit rates Intervention group at 2-months 21%, at 6-months 21%, continuous abstinence 10% Control group at 2-months 3%, at 6-months 13%, continuous abstinence 3% Significantly more intervention versus baseline patients at test site reported abstinence at 2 month follow-up (p<.0004), more patients abstinent at 6-months (P<.08). No significant differences were found at control sites.	Usual care clinicians did not receive training. Number of participants shown at the end of the intervention period.
(Miller et al. 2005), USA.	Comparative study with concurrent control n=1305 (patches) n=159 (comparison) 6-weeks Community	Quit rate at 6mth NRT (33%) versus no NRT (6%). Difference after adjustment OR=8.8, 95% CI 4.4, 17.8.	Comparison group was those who did not receive patches due to mailing error, there was a much smaller number of respondents in the comparison group.

Table 7. Controlled or Comparative Studies (Level III intervention evidence) (continued)

Author, Country	Study Design Intervention (n, duration of free supply), Setting	Results	Comment
Level III.3			
(Alberg et al. 2002; Alberg et al. 2004), USA	Comparative study without control Before-and-after study Before-and-after study. Free patches plus program versus program n=601 (before) n=311 (after) 6 weeks Community-based	Quit rate Overall quit rate was 41%, quit rate 27% higher in the classes in which free nicotine patches were offered. 38% baseline 65% at completion At 18 month follow-up there was a more rapid rate of reversion in free NRT who had quit RR=1.35, 95% CI 1.03, 1.78.	NRT part of group behavioural cessation programme. Authors note offering free patches stimulated more smokers to enrol in program and that use of patches enhanced the impact of group counselling in practice.
(Bauer et al. 2006), USA.	Comparative study Before-and-after study with historical control Random sample of n=732 (free voucher) compared with no NRT, n=515 (control) 2 weeks Community-based	Quit rate 30% free patches 6% no NRT RR=1.77 95% CI 1.17-2.68 free NRT versus no NRT.	NRT voucher for gum or patches (75% of participants) Cost effectiveness data Baseline call volume = 6 calls/day; After advertising call volume = 148 calls/day, reverted at 1 month to 6 calls/day
(Cummings et al. 2006a, Cummings et al. 2006b), USA.	Comparative study Before-and-after study (n=884) with historical control (n=515, no NRT) 2 week voucher 1,2,and 6 week mail	Quit rate Voucher 2-wk Mail 1-wk : RR=2.9 95% CI 1.9, 4.4 Mail 2-wk : RR=2.0 95% CI 1.3, 3.1 Mail 6-wk : RR=3.85 95% CI 2.6, 5.7 At the 12 month follow-up; 6-month continuous abstinence: RR=4.26 95% CI 2.48, 7.32	Data on call volume and quit rates. Quitters were those who reported smoking not at all and no cigarettes in 7 days prior to interview. Note. Results varied with choice of outcome measure but always favoured free NRT.

Table 7. Controlled or Comparative Studies (Level III intervention evidence) (continued)

Author, Country	Study Design Intervention (n, duration of free supply), Setting	Results	Comment
(Der et al. 2001), USA.	Before-and-after study n=88 12 weeks+ Clinic-based	Quit rates 36% abstinent 6mths after initial visit, 95% CI 22%, 52% if those lost to follow-up were assumed to be smoking the 6-mth abstinent rate was lower at 18%, 95% CI 11%, 28%	50% response rate at follow-up. NRT patches accounted for 63% of sample.
(Hawk et al. 2006), USA	Before-and-after study n=690 (voucher) n=230 (combination) 2-weeks Community.	Quit rates NRT Voucher 26% Quit and Win 29% Combination 27%	Quit and Win was offered with the opportunity to win a range of prizes as an intervention by itself or in combination with free NRT. Variable follow-up periods Free NRT included patches but not clear what %.
(Huang 2005), Taiwan	Before-and-after study n=10 3-months Community.	Quit rates At 9-month follow-up Abstinent 50% Decreased consumption 30%	CO breath level used as outcome measure pre-test and post-test, Free patches supplied within context of support group (n=10) to 70% of sample.
(Ivers et al. 2003), Australia.	Before-and-after study n=40 10-weeks Primary care.	Quit rates At 6-months Patches 15% Brief Intervention 1% Reduced use Patches 70% Brief Intervention 51%	Indigenous sample, 10% patches group with CO validation No one completed full course of patches Cessation rates lower than in other populations.
(Jolicoeur et al. 2000; Jolicoeur et al. 2003), USA.	Before-and-after study. Free patches plus self-help guide. n=223 Approx 6-weeks (42 patches) Community.	Overall quit rate at 6 months was 22% and 6 – weeks 21% 7-day continuous abstinence at 6-week and 6-months 12%	Defined quit as not smoked a cigarette in 7-days. Stages of change model did not predict cessation.

Table 7. Controlled or Comparative Studies (Level III intervention evidence) (continued)

Author, Country	Study Design Intervention (n, duration of free supply), Setting	Results	Comment
(Wadland et al. 1999),USA.	Comparative study Free NRT plus practice- based counselling versus free NRT plus telephone counselling n=487 10-weeks Primary care and the community.	At 6-month, quit rates (7- day smoke free status) were 35% in the practice- based group and 36% in the community-based group. An increased quit rate was noted for individuals attending 4 or more counselling sessions.	62% of the participants obtained NRT (patch or gum) with 95% opting for patches.

Table 8. Other Studies Identified by Search Strategy (Level IV intervention evidence)

Author, Country	Study Design Intervention (n, duration of free supply), Setting	Results	Comment
Level IV			
(Abdullah et al. 2006), Hong Kong	Descriptive study n=129 1-week Clinic-based	Quit rate 19% all attendees 36% all those successfully followed up at 12 months	Young smokers Type of NRT not specified but definitely included patches.
(Abdullah et al. 2004), Hong Kong	Descriptive study Smoking cessation n=841 1-week voucher Clinic	Based on intent-to-treat 7-day point prevalence quit rate at 12-month follow-up was 27%, 95% CI 25, 30%.	NRT included gum, patch or inhaler. Both patches (59%) and gum (57%) were rated as more useful than inhaler (46%).
(Jaen et al. 1997)	Descriptive study n=196 6-weeks Primary care (family practice)	Quit rate Overall at 6-month follow-up 14%	No CO validation of self-reported abstinence Additional smoking cessation materials provided differed by site.
(Mark 2003) Australia	Descriptive study Single free patch giveaway, 1 week free at 8-weeks after 7-weeks of purchasing patches Community (via pharmacies)	Readiness to quit was assessed 66% reported free patch made them seriously consider quitting smoking, 35% purchased first week, 3.6% reached final week of NRT and received 1-week of free patches	No baseline data or control. Offering free patch via pharmacies is feasible and may provide a prompt for smokers to make a quit attempt.
(Winickoff et al. 2003b), USA	Descriptive study of prospective cohort Smoking cessation programme 1-week free NRT Hospital	At 2-month follow-up, 50% of the parents reported having made a self-reported quit attempt that lasted at least 24 hours, and 20% reported tobacco abstinence	NRT patches or gum. % using patches not reported. Parents of children hospitalised with respiratory illnesses No control group.
(Winickoff et al. 2003a), USA	Descriptive study of prospective cohort Smoking cessation programme 2-week free NRT Clinic (pediatric outpatient)	At 2-month follow-up after enrolment, 56% parents reported having made a self-reported quit attempt that lasted at least 24 hours, and 18% reported tobacco abstinence (7-day).	NRT patches (51%) or gum (27%). Parents of children. No control group.

Appendix C: HTA Internet Sites

AUSTRALIA

- Centre for Clinical Effectiveness, Monash University
<http://www.med.monash.edu.au/healthservices/cce/evidence/>
- Health Economics Unit, Monash University
<http://chpe.buseco.monash.edu.au>

AUSTRIA

- Institute of Technology Assessment / HTA unit
<http://www.oecaw.ac.at/ita/welcome.htm>

CANADA

- Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) <http://www.aetmis.gouv.qc.ca/en/>
- Alberta Heritage Foundation for Medical Research (AHFMR)
<http://www.ahfmr.ab.ca/publications.html>
- Canadian Coordinating Office for Health Technology Assessment (CCHOTA) http://www.ccohta.ca/entry_e.html
- Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database <http://www.mycabot.ca>
- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University <http://www.chepe.org>
- Centre for Health Services and Policy Research (CHSPR), University of British Columbia <http://www.chspr.ubc.ca>
- Health Utilities Index (HUI)
<http://www.fhs.mcmaster.ca/hug/index.htm>
- Institute for Clinical and Evaluative Studies (ICES)
<http://www.ices.on.ca>

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA)
http://www.dihta.dk/publikationer/index_uk.asp
- Danish Institute for Health Services Research (DSI)
<http://www.dsi.dk/engelsk.html>

FINLAND

- FINOHTA <http://www.stakes.fi/finohta/e/>

FRANCE

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) <http://www.anaes.fr/>

GERMANY

- German Institute for Medical Documentation and Information (DIMDI) / HTA <http://www.dimdi.de/dynamic/en/>

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad
<http://www.gr.nl/adviezen.php>

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA)
<http://nzhta.chmeds.ac.nz/>

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM)
<http://www.oslo.sintef.no/smm/Publications/Engsmdrag/FramesetPublications.htm>

SPAIN

- Agencia de Evaluación de Tecnologías Sanitarias, Instituto de Salud “Carlos III”/Health Technology Assessment Agency (AETS)
<http://www.isciii.es/aets/>

- Catalan Agency for Health Technology Assessment (CAHTA)
<http://www.aatm.es/cgi-bin/frame.pl/ang/pu.html>

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU)
<http://www.sbu.se/www/index.asp>
- Center for Medical Health Technology Assessment
<http://www.cmt.liu.se/>

SWITZERLAND

- Swiss Network on Health Technology Assessment (SNHTA)
<http://www.snhta.ch/>

UNITED KINGDOM

- Health Technology Board for Scotland
<http://www.htbs.org.uk/Default.htm>
- National Health Service Health Technology Assessment (UK) /
National Coordinating Centre for Health Technology Assessment
(NCCHTA) <http://www.hta.nhsweb.nhs.uk/>
- University of York NHS Centre for Reviews and Dissemination
(NHS CRD) <http://www.york.ac.uk/inst/crd/>
- National Institute for Clinical Excellence (NICE)
<http://www.nice.org.uk/>

UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ)
<http://www.ahrq.gov/clinic/techix.htm>
- Harvard School of Public Health – Cost-Utility Analysis Registry
<http://www.hsph.harvard.edu/cearegistry/>
- U.S. Blue Cross/ Blue Shield Association Technology Evaluation
Center
(TEC) <http://www.bcbs.com/tec/index.html>

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