

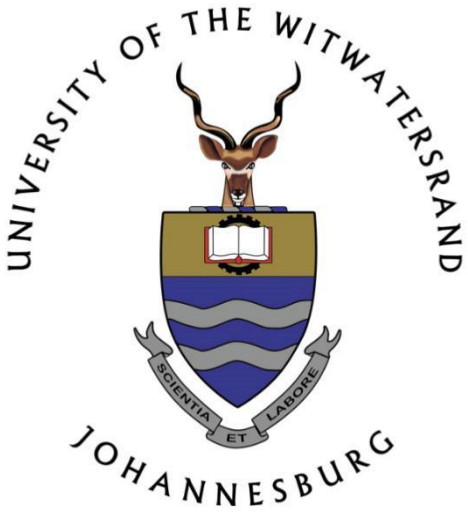
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A narrative synthesis of the cost-effectiveness studies of smoking-cessation programmes

Seninde, Ibrah Kato

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A NARRATIVE SYNTHESIS OF THE COST-EFFECTIVENESS OF SMOKING-CESSATION PROGRAMMES

A Research report submitted in partial fulfilment of the Degree of
Master of Commerce (Economics)
in the School of Economic and Business Sciences,
University of the Witwatersrand

by

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Declaration

I, Ibrah Kato Seninde, declare that this research report is my own, unaided work. It is submitted in partial fulfilment of the requirements for the degree, Master of Commerce (Economics) at the University of the Witwatersrand, Johannesburg. It has not, either in whole or in part, been submitted before for any degree or examination in this, or any other University.

Ibrah Kato Seninde

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Name of Student

IK Seninde

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Signature

14th/08/2020

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Date Submitted

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List of Abbreviations

BENESCO	Benefit of Smoking Cessation on Outcomes
CBT	Cognitive behavioural Treatment
CEA	Cost Effectiveness Analysis
CM	Contingency Management
CT	Computer-Tailored
DALY	Disability Adjusted Life Years
FDA	Food and Drug Administration
GDP	Gross Domestic Product
GP	General Practitioner
ICER	Incremental Cost effectiveness ratio
INB	Incremental Net Benefit
LIC	Low Income Countries
LMIC	Lower middle income countries
MIC	Middle income countries
NCI	National Cancer Institute
NHS	National Health Service
NRT	Nicotine replacement therapy
QALY	Quality adjusted life years
RCT	Randomized control trial
UMIC	Upper middle income countries

ABSTRACT

Objectives

Tobacco smoking remains a major public health problem from both health and economic perspectives. Although several studies have assessed the cost-effectiveness of smoking-cessation programmes, no review has estimated their incremental net benefit. This review synthesizes evidence on cost effectiveness of smoking-cessation programmes.

Methods

A literature search on cost-effectiveness of smoking-cessation programmes was conducted in the PubMed, EconLit Full-Text and Medline Complete databases. Primary studies were eligible if they conducted cost effectiveness analyses and reported incremental cost effectiveness ratios for smoking-cessation programmes. Incremental net benefits were estimated using country-specific gross national income per capita as a proxy for the willingness to pay threshold. Comparative analyses of incremental net benefit were conducted for low- and middle-income countries and for South Africa.

Results

A total of eighteen primary studies were eligible for inclusion in the review. Results show wide variation in the cost-effectiveness of smoking-cessation programmes based on the willingness to pay thresholds. Many of the interventions tailored for developed country contexts would not be economically feasible in low- and middle-income country settings.

Conclusion

The variations in study designs, outcome measures and settings make comparison difficult and thus a conclusive judgement about the cost effectiveness of smoking-cessation programmes cannot be made. Nevertheless, findings suggest that telephone counselling and pharmacotherapy-based interventions potentially yield higher health and monetary benefits when compared with low resource intensive programmes like self-help manuals; although pharmacotherapies appear relatively costly in low income country settings. This review highlights several shortcomings in methodology and transferability of the results. Efforts to develop statistical measures for pooling cost effectiveness outcomes will benefit future research.

Keywords: cost-effectiveness, smoking cessation, incremental net benefit

1.0 Introduction

Tobacco smoking remains a major public health problem as it is estimated to cost $2.25 billion in the United Kingdom, $3.5 billion in China, $6 billion in Australia and $14.7 billion in Germany (Jones et al. 2019). According to the United States (U.S) National Cancer Institute (NCI), smoking-cessation refers to the process of discontinuing tobacco smoking. Alternatively, smoking-cessation can be defined as validated sustained abstinence from cigarettes and/or other tobacco products for at least six months, but preferably for a year (Campbell, 2003).

The current health and economic burden of tobacco smoking has necessitated the need to significantly increase population level smoking cessation rates. Moreover, WHO's Director-General noted that persuading current smokers to quit "is the only way we can substantially reduce smoking-related deaths over the next 40 years" when urging countries to ratify the World Health Organization (WHO) Framework Convention on Tobacco Control (WHO FCTC) (World Health Organization, 2003).

Tobacco products in many low income countries are more diverse than those in high income countries and have different profiles of uptake and prevalence by age and gender (Prokhorov et al., 2006). Use of smokeless tobacco and forms of smoked tobacco other than cigarettes (e.g. vaping, hookahs, bidis) is more frequent in many LMICs than in HICs (NCI, 2014). This review however focuses on cigarette smoking since research on other smokeless tobacco products is limited.

In several high income countries, evidence suggests that widespread implementation of smoking cessation interventions has led to significant declines in smoking prevalence over the past years. For example, a national survey conducted in 2010 showed that 69% of adult current smokers in the United States were willing to quit and 52% of the smokers had made a quit attempt as a result of smoking cessation interventions (Center for Disease Control and Prevention (CDC, 2011). Likewise, data from a survey by the International Tobacco Control Policy Evaluation (ITC) Project determined that 38.6% of male smokers in Australia, 24.0% in the United Kingdom and 36.1% in Canada made quit attempts during the same year (Xu et al., 2019).

In contrast, cessation rates are relatively lower in developing countries since smoking cessation interventions are less affordable and accessible. For example, an investigation of 18 countries found that quit rates in developing countries ranged from 3%–18% of the population compared to over 20% in high income countries (HICs) (Jha, 2011).

Several studies link tobacco smoking and its negative health consequences with poverty. According to Hosseinpoor et al. (2012), the poor bear the highest health burden of tobacco smoking and are much more likely to die prematurely from smoking-related diseases than the rich. Evidence also suggests that the rate of death is approximately three times higher for smokers than non-smokers and the average smoker losses at least one decade of life expectancy (Jha et al., 2013). Therefore, smoking cessation potentially reduces mortality that may occur due to tobacco use and smoking related illness and yields significant health benefits. Moreover, Jha & Peto. (2014) estimated that a reduction in global smoking prevalence by one third can potentially avert over 200 million smoking-related deaths by 2025. Overall, smoking cessation reduces the risk of smoking-related morbidity and mortality.

On the other hand, the increased healthcare costs and overall decrease in productivity associated with tobacco use and smoking-related illness translates into an increased economic burden in majorly developing countries (World Health Organization, 2011). When expressed as a percentage of gross domestic product (GDP), the economic burden of smoking ranges from: 0.16% in the United Kingdom, 0.4% in Australia, 0.56% in Canada to 0.85% in the United States (Woolacott et al., 2002). Smoking-related diseases are estimated to cost the National Health Service (NHS) £1.4billion to £1.5billion a year in the United Kingdom while the United States (U.S) public health service estimates a total cost of £29 billion a year in absolute terms (Woolacott et al., 2002).

Unlike developed countries, there is limited data on the recent economic costs of smoking for developing countries. In South Africa alone, the economic cost of smoking ranged from US$ 20.2 million to US$ 127.4 million (17.6–289.6 million South African rand) from the late 1970s to 1980s (Yach et al., 1992). Another study estimated the total direct and indirect cost of smoking in South Africa at US$ 1.1 billion (2.5 billion rand), or 0.9% of GDP in 1988 (Novotny,

n.d.). Most recently, Goodchild et al. (2018) updated South Africa's smoking-attributable health expenditures (SAHE) in international dollars using the International monetary purchasing power parity (PPP) $2,397 million (1.9% of total healthcare expenditure) and total economic costs attributable to smoking at PPP$ 12,065 million (1.8% of total GDP) in 2018.

Therefore, smoking cessation potentially reduces the economic costs associated with smoking-related diseases. Moreover, Efroymson et al. (2001) suggest that redirecting the money spent on tobacco products to food and other household items can significantly reduce malnutrition by half and over 10.5 million Bangladeshis in income may be saved by poor households in developing countries.

Before implementing smoking-cessation programmes, cost-effectiveness analyses are required to determine optimal resource allocation and identify efficient programmes that support a sustainable health care system. Smoking-cessation interventions are considered cost-effective since they yield long-term health benefits such as increased life expectancy and improvements in quality of life, at a relatively low cost when compared with other health-care interventions (Boyd & Briggs, 2009).

Several programmes exist to aid smokers in cessation attempts. These are mainly classified as pharmaco-therapy (drug treatments) or behavioral-therapy based programmes (Ruger & Lazar, 2012). Pharmacotherapies include: nicotine-based medications (gum, patch, inhaler, nasal spray, sublingual lozenge), bupropion, varenicline, clonidine and nortriptyline as approved by the U.S Food and Drug administration (FDA). Other pharmacotherapies that are not approved by the FDA include: selegiline, moclobemide, rimonabant, doxepin, fluoxetine, sertraline, paroxetine and naltrexone. Behavioral therapies include: self-help, intensive counselling, psychological counselling, telephone counselling, professional advice, partner support. Table 1 summarizes the interventions for smoking cessation.

Table 1: Interventions for smoking-cessation

Pharmacotherapies			**Behavioral therapies**
First-line drugs	**Second-line drugs**	**Other drugs not FDA approved for smoking cessation**	
Nicotine-based medications • Nicotine gum • Nicotine patch • Nicotine inhaler • Nicotine nasal spray • Nicotine sublingual lozenge Non nicotine-based medications • Antagonist (e.g., bupropion) • Partial agonist (e.g., varenicline)	Clonidine Nortriptyline	Fluoxetine Sertraline Paroxetine Naltrexone Rimonabant Doxepin Moclobemide Selegiline	Partner support Self-help Psychological counseling • Telephone counseling • Professional advice • Intensive counseling

Adapted from (Ruger & Lazar, 2012)

Unlike developed country settings, primary studies on the cost effectiveness of smoking cessation programmes for low and middle income country settings are limited. For this reason, decision makers in developing countries may benefit from studies that review and synthesize the existing literature from already conducted primary cost effectiveness analyses. Several studies have reviewed evidence on smoking-cessation programmes. Song et al. (2002) reviewed the cost-effectiveness of pharmacological interventions for smoking-cessation. Results from the review indicated that, compared to advice or counseling alone, the incremental cost per life years saved ranged from: $1,441 to $3,455 for nicotine replacement therapy (NRT), $920 to $2,150 for bupropion and $1,282 to $2,836 for NRT plus bupropion.

Ronckers et al. (2005) re-calculated the cost-effectiveness ratios of 28 studies for smoking-cessation. Findings from the study suggested that standardization of programme effects increases cost effectiveness ratios and decreases intervention effects. Gordon et al. (2007) reviewed the cost-effectiveness of face-to-face behavioral interventions for smoking-cessation. The review analyzed cost-effectiveness results of sixty-four studies from the year 1995 to 2005. The findings

suggested that incremental cost-effectiveness for face-to-face behavioral therapies for smoking cessation are consistently low; less than €14,000 per quality-adjusted life-year gained for smoking-cessation programmes compared to certain preventive pharmaceutical and invasive interventions.

Lastly, Ruger & Lazar (2012) conducted a systematic review of evidence on cost-effectiveness of pharmacotherapies and behavioral therapies for smoking-cessation. Results from the study demonstrated that incremental cost-effectiveness ratios for various smoking-cessation programmes vary greatly depending on contextual factors.

Overall, none of the existing reviews estimated the incremental net benefit for smoking-cessation programmes. Instead, all the existing reviews used the incremental cost effectiveness ratio (ICER) approach to analyze the cost effectiveness of smoking cessation programmes. However, this approach has been criticized for its weaknesses and the incremental net benefit (INB) approach has been proposed as a better alternative (Stinnett & Mullahy, 1998). These weaknesses include the following;

Since two opposite results can yield the same ICER, interpreting these estimates may be difficult and quite confusing for decision makers. For example, in an evaluation of two programmes, a programme with a negative ICER is cost effective if it falls in the south west quadrant but not the north east of the cost effectiveness plane. Similarly, a programme with a positive ICER which is lower than the cost effectiveness threshold is cost effective if it falls in the northeast quadrant, but not in the south-west quadrant of the cost effectiveness plane. For evaluations comparing three or more programmes, this decision may be unintuitive since the most cost effective programme yields the ICER that falls below the cost effectiveness threshold. In contrast, interpreting estimates from the INB approach is straightforward: the intervention that yields a positive INB is considered cost effective while an intervention that yields a negative INB is not cost effective (Paulden, 2020).

Secondly, decision makers may desire to rank more than two programmes rather than one single cost effective alternative. In this regard, using ICERs makes it difficult to rank the cost

effectiveness of programmes because a higher or lower ICER does not necessarily mean that a programme is more cost effective that the other. In contrast, incremental net benefit can be used to rank cost effectiveness of multiple programmes since the higher the INB, the more cost effective the programme (Paulden, 2020).

In addition, estimating confidence intervals for ICERs based on a normal distribution may be invalid since it is a discontinuous measure (Crespo et al., 2014). Even if reported, interpreting a confidence interval for an ICER may be difficult since a high or low ICER may not necessarily represent the relative cost effectiveness of an intervention in comparison to others. By contrast, the INB has a normal distribution which easily allows for conducting probabilistic analyses and interpretation of its confidence intervals is straightforward. Moreover, this also allows for pooling of cost effectiveness evidence which can help inform decision making in resource constrained countries that lack economic evaluation studies. That is to say, (Crespo et al., 2014) developed a meta-analysis method (Comparative Efficiency Research-COMER) that combines cost effectiveness studies by pooling the INB.

Nevertheless, both the ICER and INB approach remain useful for conducting economic evaluations of healthcare programmes. However, the INB approach remains a better method to inform allocation decisions since outcomes are reported in monetary terms which can easily be used to determine the return on investment from an intervention compared to other programmes. Therefore, in addition to its other advantages: the INB approach is easier to interpret, allows for conducting probability analyses, allows for ranking cost effectiveness of two or more programmes and allows for combining cost effectiveness evidence in a meta-analysis. For these reasons, this review supplements the existing literature by estimating the incremental net benefit of various smoking-cessation programmes.

The objectives of the study were:

(a) To estimate the incremental net benefit of smoking-cessation programmes.

(b) To assess the cost-effectiveness of smoking-cessation programmes depending on willingness to pay thresholds for: low income countries (LICs), middle income countries (MICs) and South Africa.

2.0 Theoretical framework

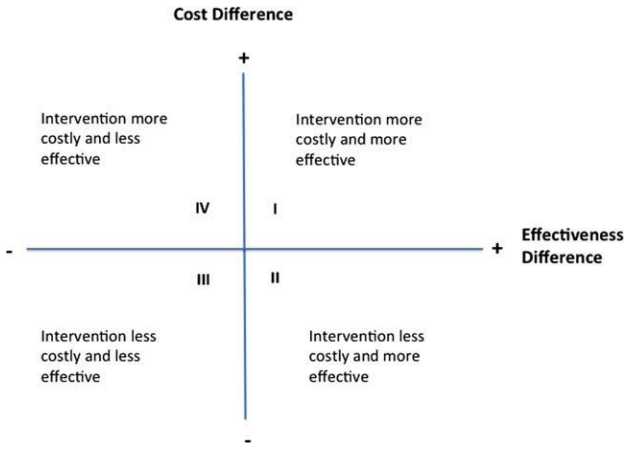
By definition, cost effectiveness analysis (CEA) is the evaluation of costs and consequences of alternative interventions using clinical outcomes in natural units such as: cost per quality adjusted life years (QALYs) gained (Rudmik & Drummond, 2013). The incremental cost-effectiveness ratio (ICER) refers to the additional cost that one programme imposes compared to the additional effect. That is to say;

$$ICER = \frac{(C_{1-}\ C_0\ )}{(E_1 - E_0\ )}$$

Where: C_1 and E_1 represent the cost and effect in the intervention group and C_0 and E_0 represent the cost and effect in the control group respectively. Costs are usually represented in monetary units, while effects can be measured in health status (Quality Adjusted Life Years saved, Life Years Saved, Disability Adjusted Life Years) or another outcome of interest (quit rate, abstinence rate).

Policy makers aim to implement the programme with the lowest ICER although other factors may be considered. For example, affordability from the patient's perspective may influence policy makers to implement a programme with a high ICER. Cost effectiveness outcomes can be presented by a cost effectiveness plane as illustrated in figure 1; adapted from (Rudmik & Drummond, 2013).

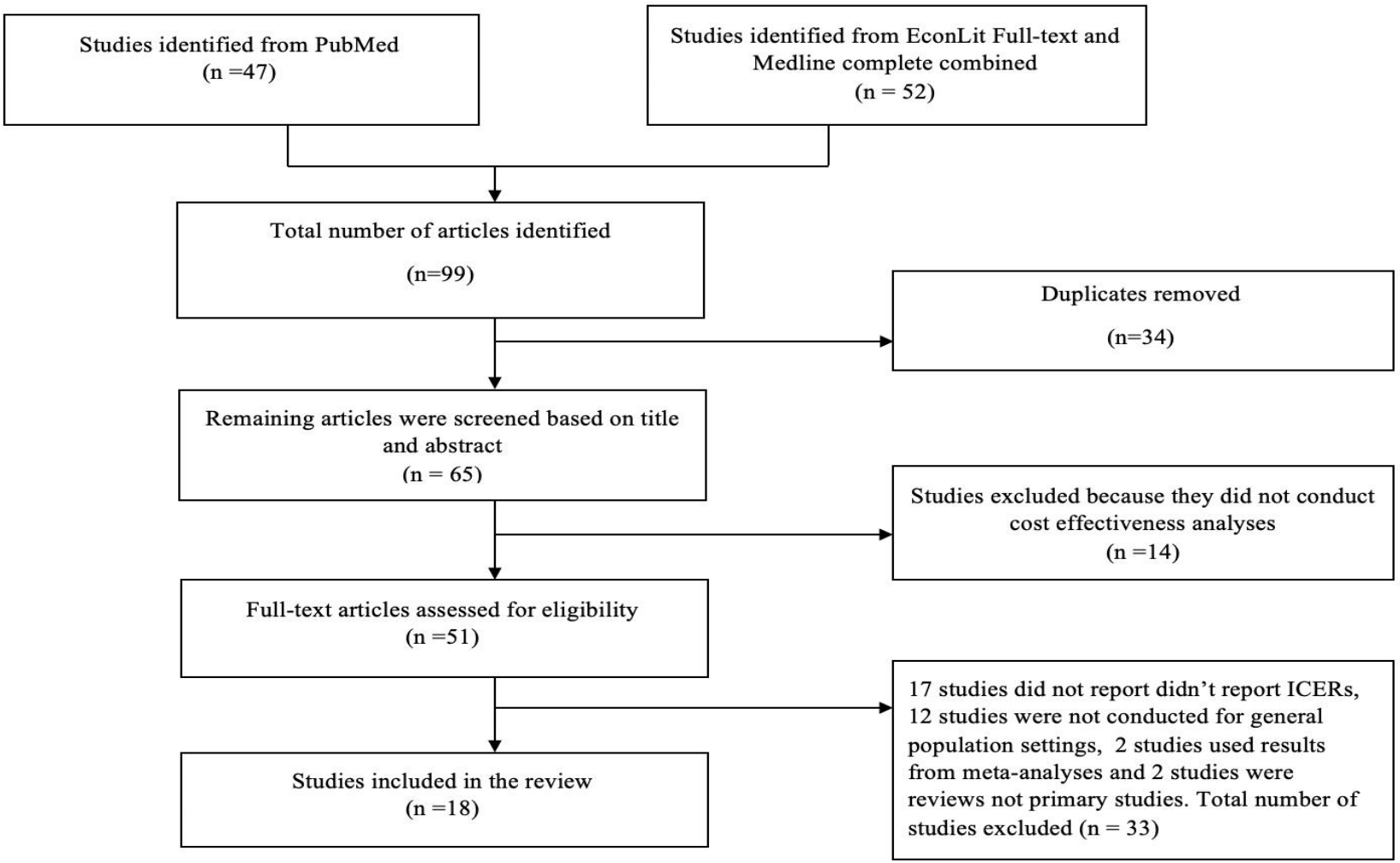
Figure 1: A cost effectiveness plane



Programmes that fall in in either quadrant (ii) or (iv) are considered dominant and they do not need ICERs to be calculated as they are either more effective and less costly (ii) or more expensive and less effective (iv). Programs that have lower costs and higher benefits -quadrant (ii) are usually accepted while; programs that have higher cost and lower benefit quadrant (iv) are rejected. Since programs in quadrant (i) have higher cost and higher benefit, and those that fall in quadrant (iii) have lower cost and lower benefit, ICERs have to be calculated and compared.

The decision to choose the most cost-effective program within quadrant (i) and quadrant (iii) depends on the maximum ICER for which policy makers are willing to accept. This involves calculating the incremental net benefit which depends on the willingness to pay threshold for additional benefit yielded (Rudmik & Drummond, 2013). The willingness to pay threshold represents how much policy makers will pay to gain one extra unit of health outcome (Stinnett & Mullahy, 1998). The incremental net benefit is calculated as; [Maximum willingness to pay x Incremental effectiveness] - Incremental cost. A programme is considered cost-effective (not cost effective) if the incremental net benefit is positive (negative) (Willan, 2004).

Figure 2: Flow chart showing the study selection process



3.0 Methodology

3.0.1 Search strategy and study selection

A literature search was conducted in the PubMed, EconLit Full-Text, Medline Complete databases and the reference list of one comprehensive and updated systematic review (Ruger & Lazar, 2012). The electronic search included the term(s), "smoking cessation" in the title or abstract, "cost effectiveness" in the title, and "incremental cost effectiveness ratios" in all fields to identify published cost effectiveness analyses on smoking-cessation interventions or programmes. Inclusion criterion was cost effectiveness analysis and cost utility analysis of smoking-cessation programmes/interventions. The initial search identified 99 articles in total from all databases: 47 articles from PubMed, 52 articles from Medline Complete and EconLit Full-Text combined. 34 duplicate results were removed. The remaining 65 results were screened for eligibility based on title, abstract, and, where necessary, full texts were obtained.

For the purpose of this study, investigations were limited to cost effectiveness and cost utility analyses in case they reported ICERs. Unlike cost minimization analyses, cost effectiveness and cost utility analyses evaluate cost and outcomes of programmes using "natural" units: Quality Adjusted Life Years (QALYs), Life Years Saved (LYS) and Disability Adjusted Life Years (DALYs). It should be noted that quality of life measures (QALYs, LYG and DALYs) are the recommended health outcome measures for use when estimating the incremental net benefit (Stinnett & Mullahy, 1998). Most importantly, CEAs and CUAs report the incremental cost effectiveness ratio which has several methodological commonalities with the incremental net benefit measure in contrast to other economic evaluation methods. Both the ICER and INB are calculated using common parameters as described in the theoretical framework section of this study.

For this reason, 14 studies were excluded because they did not conduct cost effectiveness analyses or cost utility analyses based on title and abstract. Full texts of the remaining 51 articles were then obtained and further screened for eligibility: 17 studies did not report ICERs, 12 studies were not conducted in a general population setting, 2 studies used results from meta-analyses and 2 studies were reviews not primary studies. Therefore, a total of 33 studies were excluded leaving 18 studies for inclusion. The study selection process is summarized in figure 2.

3.0.2 Data extraction

Eighteen full-text copies of primary studies that met the eligibility criteria were obtained and data were extracted. Data extracted included study design (observational survey, randomized control trial, markov model), population setting, intervention, time horizon, main outcome or benefit measure (QALYS, DALYs), cost components and incremental cost effectiveness ratios as illustrated in table 2; adapted from (Ruger & Lazar, 2012). A supplementary excel spreadsheet of the initial data extracted is available upon request.

Table 2: Data extraction form

1. Author
2. Year of study
3. Country
4. Year of publication
5. Study design
6. Intervention
7. Comparator
8. Health outcome measure
9. Cost perspective
10. Base year for price estimates
11. Currency
12. Incremental cost
13. Incremental effect
14. Incremental cost effectiveness ratio
15. Country specific GDP per capita income (2016)
16. Consumer price index (2016)

Adapted from (Ruger & Lazar, 2012)

3.0.3 Data synthesis and analysis

It was earlier anticipated that the review would adopt a meta-analysis by pooling the calculated INB estimates of the included studies as seen in one meta-analysis (Haider et al., 2019), however; this approach was not feasible since majority of the primary studies included did not report variance estimates and confidence intervals for the cost outcomes which are a factor for conducting a meta-analysis. In addition, a meta-analysis of a subset of data from included studies was still not feasible since the studies varied widely in terms of study designs and health

outcomes. For these reasons, a narrative synthesis was conducted since other intuitive statistical and econometric analyses that are commonly used in economic evaluations were also deemed unnecessary for this study.

This review further re-calculated incremental cost-effectiveness ratios (ICERs) and estimated incremental net benefit (INB) of smoking-cessation programmes using data extracted from primary studies. Information relating to population, country, cost perspective, interventions, health outcome measure and key findings of the included studies were summarized and presented in table 3 for discussion of the evidence. Incremental net benefit values were estimated for using the equation: [maximum willingness to pay x incremental effectiveness] - incremental cost. All calculations and cost adjustments were done using Microsoft Excel 2010.

Despite the challenges regarding transferability of the findings from economic evaluations conducted in developed countries to developing country settings (M. Drummond et al., 2015), cost-effectiveness comparisons were made for low- and middle-income countries and South Africa.

Costs that were originally published in other currencies were converted to U.S dollars using the base year exchange rate obtained from the World Bank website (https://data.worldbank.org/). All cost data were adjusted to 2016 U.S dollar values using the country specific consumer price index (CPI) obtained from the Word Bank website (https://data.worldbank.org/) as below.

$$value\ in\ 2016\ (U.S\ dollars) = value\ in\ base\ year\ \left(\frac{consumer\ price\ index\ in\ 2016}{consumer\ price\ index\ in\ base\ year}\right)$$

Programmes that yield a positive (negative) incremental net benefit were considered cost-effective (non-cost-effective). Based on the World Health Organization's Choosing Interventions that are Cost–Effective criteria (Marseille et al., 2014), willingness to pay threshold used was: $253 for low income countries (LICs), $683 for lower middle-income countries (LMICs), $2642 for upper middle-income countries (UMICs) and $1757for South Africa. It should be noted that these willingness to pay thresholds represent the equivalent of three times less the gross national

income per capita values of the given country settings as suggested by the World Health Organization (Marseille et al., 2014). For example, this implies that an individual in a low income country setting is willing to pay $253 per unit reduction in mortality risk or gain in an additional life year.

Table 3: Summary of cost effectiveness of smoking-cessation programmes

Characteristics	(Akers et al. 2007)	(Kaper et al. 2006)	(López-Núñez et al. 2016)
Study design	Randomized control trial	Randomized control trial	Randomized control trial
Country	United States	Netherlands	Spain
Population setting	1069 smokers who called on a quit-line who were older than 15 years	General population of smokers ≥ 18 years (n=1266)	Smokers in Spain ≥ 18 years who smoke ≥ 10 cigarettes per day
Intervention	(1)-Assisted self-help (manual plus a videotape and phone counselling) (2)- manual only (a self-help manual)	Re-imbursement for smoking-cessation treatment (SCT) costs	(1)- Cognitive behavioral treatment (CBT) (2)- Contingency management protocol (CM) + (CBT)
Comparator	(1)-manual only (a self-help manual) (2)- Assisted self-help	No re-imbursement	(1)- Voucher-based contingency management protocol (CM) (2)- Standard care
Perspective	Societal perspective	Dutch societal perspective	Spanish Government Perspective
Time Horizon	18 months	6 months	21 months
Main outcome	Quit rate	Quality adjusted life years	Abstinence rate
Cost components	Intervention costs	Treatment costs	Costs of healthcare
Base year costs	2000	2002	2016
Summary results	(1)-Assisted self-help costs $451 per additional quitter compared with the manual only intervention. (2)-compared with assisted self-help, the manual only programme is more cost-effective with an incremental cost of $374 per additional quitter.	Re-imbursement for SCT costs increased the quit rate among motivated quitters: ICER was $56 when compared with no re-imbursement for SCT costs	Adding a voucher-based CM protocol to CBT costs $201 per additional quitter when compared with standard care (mix of all current drug and behavioral interventions) and CBT alone. CBT alone is more cost-effective with a lower incremental cost of $75 per additional quitter when compared with CM alone

Table 3: Summary of cost effectiveness of smoking-cessation programmes (continued)

Characteristics	(Hall et al., 2005)	(Shearer and Shanahan 2006)	(Stanczyk et al. 2014)
Study design	Randomized control trial	Randomized control trial	Randomized control trial
Country	United States	Australia	Netherlands
Population setting	Smokers > 18 years (> 10 cigarettes per day) who are motivated to quit	Existing smokers in Australia (n=44)	Daily smokers, 18 years or older, motivated to quit smoking within the following six months and had internet access
Intervention	(1)- Bupropion (2)- Nortriptyline (3)- Psychological Intervention	(1)-Telephone counselling (2)- NRT plus GP counselling (3)- NRT plus proactive telephone counselling ((4)- Bupropion plus GP counselling (5)- Bupropion plus proactive telephone counselling (6)- Bupropion plus NRT with GP counselling	(1)- Video-based computer- tailored intervention (2)- Text-based computer -tailored intervention
Comparator	Placebo	(1)- Brief advice (2)- Proactive telephone counselling (3)- NRT plus GP counselling. (4)- Placebo plus GP counselling (5)- Bupropion plus GP counselling (6)- NRT plus GP counselling	General text-based advice
Perspective	Payer's perspective	Government perspective	Societal perspective
Time Horizon	52 weeks	≥ 6 months	12 months
Main outcome	Quit rate	Quit rate	Quality adjusted life years
Cost components	Treatment costs	Cost of treatment	Intervention and healthcare related costs
Base year costs	2000	2003	2013
Summary results	Psychological therapy combined with medical management cost less than the two drug treatments, and was more cost-effective: incremental cost of $164 per additional quitter compared with placebo. Nortriptyline was more cost-effective than bupropion compared with a placebo: ICER of $276 and $563 per quitter respectively	Combined with nicotine replacement therapy alone, telephone counseling was cost-effective with an incremental cost of $70 per additional. Bupropion combined with NRT were dominated compared with telephone counselling since the interventions were more costly and less effective	video-based CT intervention cost $1,008 per additional QALY compared with general text-based advice Text-based computer tailored intervention was dominated

Table 3: Summary of cost effectiveness of smoking-cessation programmes (continued)

Characteristics	(Stapleton et al., 1999)	(Pinget et al. 2007)	(Wu et al. 2014)
Study design	Randomized control trial	Randomized control trial and Markov model	Randomized control trial and markov model
Country	United kingdom	Switzerland	United Kingdom
Population setting	Dependent smokers (who smoke more than 14 cigarettes per day) who were motivated to stop, aged 18 years and above (n= 724)	Swiss university physicians (residents) were randomized to receive training in smoking interventions or a control educational intervention	Adult smokers aged 18–65 years identified from the records of 123 MRC General Practice Research Framework practices.
Intervention	Transdermal nicotine patch	Physician training in smoking cessation counselling	Computer-tailored self-help
Comparator	GP counselling	No training	Generic self-help
Perspective	National Health insurance perspective	Third-party payer perspective	National Health Service (NHS)/ Personal Social Services (PSS) perspective
Time Horizon	12 months	1 year	6 months
Main outcome	Life years saved	Life years saved	Quality adjusted life years
Cost components	Cost of treatment (counselling time, nicotine patches , patient booklets)	Costs of training physicians	Intervention and healthcare-related costs
Base year costs	1998	2003	2009
Summary results	Transdermal nicotine patch cost $329 per additional life year saved compared with GP counselling	The physician training programme was a dominant intervention with an ICER of -$17 when compared with no training (intervention was less costly and more effective)	The computer-tailored intervention was slightly more cost effective than generic self- help. Smokers in the intervention group gained 0.0006 additional QALYs at an incremental cost of $6 which yielded an ICER of $11600 per QALY.

Table 3: Summary of cost effectiveness of smoking-cessation programmes (continued)

Characteristics	(Cadier et al. 2016)	(Lal et al. 2014)	(Németh et al. 2018)
Study design	Markov Model	Markov model	EQUIPTMOD Markov model
Country	France	Australia	Hungary
Population setting	French smokers (defined as ≥1 cigarette/day) aged 15–75 years (n=1000)	Smokers in Queensland, Western Australia and the Northern Territory aged 35–100 years	General population of Hungarian smokers ≥ 18 years
Intervention	Full (free) medical coverage of intervention	Proactive telephone counselling (call-back counselling)	(1)-Social marketing campaign (Scenario A) (2)-Behavioural support therapies and proactive telephone support (Scenario B) (3)- combination of the two scenarios (A and B)
Comparator	€50 coverage	Face to face counselling	current practice (existing legislation that bans indoor smoking; brief physician)
Perspective	French Statutory Health Insurance	Societal perspective	Health provider perspective
Time Horizon	5 years	100 years	Lifetime
Main outcome	Life years saved	Disability adjusted life years saved	Quality adjusted life years gained
Cost components	Intervention costs	Intervention costs and projected healthcare costs in absence of the intervention	Programme costs
Base year costs	2009	2010	2017
Summary results	Full (free) coverage of smoking-cessation treatment costs $7,769 per additional life year saved when compared with providing a €50 coverage program in the base-case scenario	Proactive telephone counselling is dominant when compared with no call-back counselling. Incremental cost effectiveness for proactive telephone counselling per additional quitter is estimated at $818 per DALY compared with face to face counselling.	Introducing a social marketing campaign costs $6,725 per additional QALY when compared with current practice. Scenario B and the combination of scenario A and B are both dominant over current practice.

Table 3: Summary of cost effectiveness of smoking-cessation programmes (continued)

Characteristics	(Cornuz et al., 2006)	(Feenstra et al. 2005)	(von Wartburg et al., 2014)
Study design	Markov model	Dynamic model	BENESCO model
Country	Canada, France , United Kingdom , United States , Spain, Switzerland	Netherlands	Canada
Population setting	Simulated cohorts of smokers in 6 western countries who smoked (≥ 20 Cigarettes) and sought the interventions	Dutch smokers who are ≥18 years	Current smokers who seriously consider quitting within the next 30 days
Intervention	(1)- Nicotine gum (2)- Nicotine patch (3)- Nicotine spray (4)- Nicotine inhaler (5)- Bupropion	(1)- Minimal counselling(MC) + NRT (2)- Intensive counselling (IC)+ NRT (3)- Intensive counselling (IC)+ bupropion (4)- Telephone counselling	Varenicline (extended course)
Comparator	GP counselling	Current practice (mix of all current initiatives to stop smoking in Netherlands)	(1)- Bupropion (2)- Nicotine replacement therapy (NRT) (3)- Unaided cessation (standard course)
Perspective	Third-party payer's perspective	Dutch National Health Insurance	Societal perspective
Time Horizon	3 months	1 year	Lifetime
Main outcome	Life years saved	Quality adjusted life years	(1)-Quality adjusted life years (2)-Quit rates
Cost components	Medical and non-medical costs for smoking cessation	Program costs	Direct healthcare costs of the intervention
Base year costs	2003	2000	2009
Summary results	Incremental cost per life years saved range: (from lowest to highest) Gum: $147 in Spain to $2,812 in USA Patch: $116 in France to $2,485 in UK Spray: $129 in Spain to $2,932 in USA Inhaler: $504 in France to $2,827 USA Bupropion: $40 in Spain to $1,075 in USA	Compared to current practice, minimal GP counselling is dominant. Incremental cost per QALY is: $52 for telephone counselling, $72 for minimal counselling when combined with NRT, $199 for intensive counselling plus bupropion and $295 for intensive counselling added to NRT	Compared with bupropion and NRT interventions, varenicline is dominated (less costly and less effective) Similarly, varenicline is dominated compared with unaided cessation

Table 3: Summary of cost effectiveness of smoking-cessation programmes (continued)

Characteristics	(Heitjan et al., 2008)	(Boyd and Briggs 2009)	(Tran et al., 2002)
Study design	Monte-Carlo simulation model	Observational study	Observational study
Country	United States	Scotland	United States
Population setting	General population	Smokers aged 18+ years who accessed cessation services between March and May 2007	Smokers aged 21–70 years, who had tried at least once to quit smoking.
Intervention	(1)- Bupropion (2)- Varenicline	(1)-Pharmacy-based support (2)- Group Counselling	Pharmacist directed programme (1)- Nicotine Patch (2)- Nicotine gum (3)- Bupropion
Comparator	(1)- No treatment (2)- Bupropion (3)- Bupropion with Tailored Therapy	Self-quit	Self-directed quit attempt
Perspective	Payer's perspective	National Health Service	Payer perspective
Time Horizon	1 year	52 weeks	1 Year
Main outcome	Life years saved	Quality adjusted life years	(1)-QALYs (2)-Life years saved
Cost components	Costs of smoking-cessation treatment	Intervention costs	Program costs
Base year costs	2007	2007	1997
Summary results	Bupropion costs $690 per additional life years saved compared with no treatment. Varenicline costs $1,352 compared with bupropion alone. Varenicline costs much lower: $456 when compared with a combination of bupropion and tailored therapy	Compared to self-quit, the additional cost per quality adjusted life year (QALY) gained is approximately: $905 for the pharmacy-based support program, $1,134 for group-based support counselling.	Compared with self-directed quit attempt, nicotine patch costs $505 per QALY, nicotine gum cost $664 per additional QALY and bupropion costs $620 per additional QALY. Results suggested that nicotine patch was the most cost-effective intervention compared with self-directed quit attempt

4.0 Results

This section presents cost effectiveness results in a narrative way. Eighteen primary studies that conducted cost effectiveness analysis of smoking-cessation programmes were included. Interventions included nicotine gum, nicotine patch, nicotine inhaler, nicotine nasal spray, nortriptyline, self-help, telephone counselling, and intensive general practitioner counselling.

Study designs varied across studies: Seven studies conducted a cost effectiveness analysis (CEA) using a randomized control trial (RCT) study design, two studies used both RCT and markov model, four studies used markov modelling approach only, one study used a dynamic model, one study used the Benefits of Smoking Cessation on Outcomes (BENESCO) model, one study used Monte-Carlo simulation and two studies used observational survey.

Studies were conducted from six perspectives: five studies were conducted from the societal perspective, two studies from the government perspective, three studies were conducted from the payer's perspective, two studies from the third-party payer's perspective, five studies were conducted from the National health Insurance (NHI) perspective and one study was conducted from the healthcare provider perspective.

Outcome measures also differed between studies: six studies measured quality adjusted life years (QALYs), six studies measured life years gained/saved (LYG/LYS), four studies measured quit rates/abstinence rates, one study measured disability adjusted life years (DALYs) and one study measured both QALYS and quit rates. Subsequently, a detailed description of primary study outcomes summarized in table 3 is presented in order beginning with randomized control trials (RCTs), followed by simulation models and lastly observation study designs.

Seven cost effectiveness analyses used a randomized control trial (RCT); RCTs limit the bias in clinical trials and thus they are considered the "gold standard" of clinical outcomes (Weinstein et al., 1996). One study that randomized 1,069 participants assessed the cost-effectiveness of two low-intensity programmes: manual only (a self-help manual) and assisted self-help (manual plus a video-tape and two supportive phone calls from tobacco-cessation counsellors) for smoking cessation in the United States. Compared with assisted self-help, the manual only programme

was more cost-effective with an incremental cost of $374 per additional quitter. The assisted self-help programme cost $451 per additional quitter compared with the manual only intervention (Akers et al., 2007).

Results from another randomized control trial conducted among Dutch smokers suggested that re-imbursement of smoking-cessation treatment increased the quit rate among motivated quitters with an incremental cost effectiveness ratio of $56 when compared with no re-imbursement (Kaper et al., 2006).

According to López-Núñez et al. (2016), adding a voucher-based contingency management (CM) protocol to cognitive behavioral treatment (CBT) for smoking cessation is cost-effective compared to CBT alone. The CBT programme includes: behavioral contracts, nicotine fading, self-monitoring of consumption, physiological feedback consumption, and relapse prevention strategies while the CM programme includes reinforcing nicotine abstinence through a voucher programme with a reset contingency. Adding a voucher-based CM protocol to CBT costs $201 per additional quitter when compared with standard care (mix of all current drug and behavioral interventions) and CBT alone. However, CBT alone is more cost-effective with a lower incremental cost of $75 per additional quitter when compared with CM alone.

Hall et al. (2005) compared the cost-effectiveness of two drug treatments (bupropion, nortriptyline) and psychological therapy combined with medical management using two exploratory analyses: (bupropion versus nortriptyline versus placebo) by (medical management alone versus medical management plus psychological intervention). Results from the trial suggested that psychological therapy combined with medical management costs less than the two drug treatments, and is more cost-effective: incremental cost of $164 per additional quitter compared to placebo. In addition, nortriptyline costs $276 per additional quitter while bupropion costs $563 per quitter.

One randomized trial estimated the cost-effectiveness of four interventions in Australia: brief advice, telephone counselling, nicotine replacement therapy, bupropion. Combined with nicotine replacement therapy alone, telephone counselling was cost-effective with an incremental cost of

$70 per additional quitter. Bupropion combined with NRT were dominated compared with telephone counselling since the interventions were more costly and less effective (Shearer and Shanahan, 2006).

Evidence from another randomized control trial suggested that video-based computer-tailored (CT) intervention is more cost-effective compared with general text-based advice. From a societal perspective, the economic evaluation measured: intervention, productivity, respondent and health care related costs. Text-based tailored intervention was dominated when compared with general text-based advice. Video-based CT intervention costs $1,008 per additional compared with general text based advice at a 12 moths follow up (Stanczyk et al., 2014).

Another randomized control trial estimated the incremental cost-effectiveness of transdermal nicotine patches in the United Kingdom. The study found that prescribing transdermal nicotine patches for smoking cessation is cost-effective with an incremental cost of $329 per life year saved compared with general practitioner (GP) counselling (Stapleton et al., 1999).

Two studies used both randomized control trial and markov modelling approach for assessing cost-effectiveness of smoking-cessation programmes. The first study evaluated the cost-effectiveness of a physician training programme in primary care for smoking-cessation. Results from the study suggested that training physicians is dominant (intervention is less costly and more effective) with an ICER of -$17 when compared with no training (Pinget et al., 2007). The second CEA compared the incremental cost-effectiveness of a computer-tailored self-help intervention with a generic self-help intervention for smoking cessation. Results from the study demonstrated that computer-tailored intervention is more cost-effective than generic self-help: computer-tailored intervention costs $11,600 per additional QALY (Wu et al., 2014).

Four studies used markov models; one CEA estimated the incremental cost effectiveness ratio (ICER) of providing free (full coverage) smoking-cessation treatment to motivated smokers aged 15 to 75 years of age in France. Assuming full (free) coverage of smoking-cessation treatment, the programme would cost $7,769 when compared with providing a €50 coverage program in the base case scenario (Cadier et al., 2016).

Another study used a markov model to assess the cost-effectiveness of a quit-line call-back counselling service for smoking-cessation compared with face to face counselling in Western Australia. Over a life-time horizon, results suggested that the introduction of a quit-line call-back counselling service can be cost-effective as well as lead to health status improvements; call-back counselling is dominant when compared with no call-back counselling. In addition, the incremental cost effectiveness for call-back counselling per additional quitter is estimated at $818 per DALY compared with face to face counselling in Australia (Lal et al., 2014).

A third study used the EQUIPTMOD markov model to evaluate the incremental cost-effectiveness of three implementation scenarios in Hungary: (a) introducing a social marketing campaign; (b) doubling the reach of existing group-based behavioral support therapies and proactive telephone support; and (c) a combination of the two scenarios compared with current practice (existing legislation that bans indoor smoking; brief physician counselling). Introducing a social marketing campaign costs $6,725 per additional QALY gained compared with current practice. Scenario B and the combination of scenario (A and B) are both dominant over current practice. The results suggested that introducing a social marketing campaign to curb smoking would be cost-effective while doubling the coverage of existing group-based behavioral support therapies and proactive telephone support (Németh et al., 2018).

A multi-national study estimated the incremental costs effectiveness ratio of first-line pharmacotherapies (nicotine inhaler, patch, gum, spray and bupropion) for smoking-cessation across six countries: Spain, Canada, France, United States, Switzerland and United Kingdom. The incremental cost per additional life year saved ranged from (lowest to highest): $147 in Spain to $2,812 in the United States for nicotine gum, $116 in France to $2,485 in the United Kingdom for nicotine patch, $129 in Spain to $2,932 in the United States for nicotine spray, $504 in France to $2,827 in the United States for nicotine inhaler and $40 in Spain to $1,075 in the United States for bupropion (Cornuz et al., 2006).

One dynamic modelling study conducted in the Netherlands estimated the cost-effectiveness of five face to face smoking-cessation interventions (minimal general practitioner counselling with

or without nicotine replacement therapy (NRT), intensive counselling (IC) with NRT or bupropion and telephone counselling all compared with current practice (mix of all current initiatives to stop smoking in Netherlands). Future gains in quality adjusted life years saved were projected over a time horizon of 75 years. Results demonstrated that minimal GP counselling is dominant compared with current practice since it has lower (negative cost) incremental cost and yields positive effect. For other interventions, incremental cost per life year saved ranged from approximately $52 for telephone counselling, $72 for minimal counselling when combined with NRT, $199 for intensive counselling plus bupropion to $295 for intensive counselling added to NRT (Feenstra et al., 2005).

Another CEA evaluated the long-term cost-effectiveness of varenicline compared with other smoking-cessation programmes in Canada using the Benefits of Smoking Cessation on Outcomes (BENESCO) model. Compared with bupropion and NRT, varenicline is dominated (less costly and less effective) with an incremental cost of -$26 and -$58 per QALY respectively. Similarly, varenicline is dominated compared with unaided cessation with an incremental cost of -$28 per QALY (von Wartburg et al., 2014).

Heitjan et al. (2008) used Monte-Carlo simulation to estimate the cost-effectiveness of three drug treatments for smoking-cessation: transdermal nicotine (tailored therapy), varenicline and bupropion. Results suggested that bupropion is dominant (more effective and less expensive) over transdermal nicotine. Bupropion costs $690 per additional life years saved compared with no treatment. Varenicline costs $1,352 compared with bupropion alone. Varenicline costs much lower: $456 when compared with a combination of bupropion and tailored therapy.

Two studies used observational surveys. One observational study from the National Health Service (NHS) in Glasgow evaluated the cost-effectiveness of offering one to one pharmacy-based counselling and group-based support for smoking-cessation. Compared to self-quit, the additional cost per QALY gained is: $905 for the pharmacy-based support program, $1,134 for group-based support counselling at a 1-year post-quit time horizon in Scotland (Boyd & Briggs, 2009).

Another observational study evaluated the incremental cost-effectiveness of a pharmacist-directed smoking-cessation programme in the United States. Compared with self-directed quit attempt, nicotine patch cost $505 per additional QALY, nicotine gum cost $664 per additional QALY and bupropion cost $620 per additional QALY. Results suggested that nicotine patch is the most cost effective intervention compared with self-directed quit attempt (Tran et al., 2002).

Table 4: Cost effectiveness estimates of smoking cessation programmes for developing countries

Study	Intervention	Comparator	Outcome measure	Incremental Cost (U.S Dollars)	Incremental Effect	ICER	INB for LICs (U.S Dollars)	INB for LMICs (U.S Dollars)	INB for UMICs (U.S Dollars)	INB for South Africa (U.S Dollars)
(Feenstra et al. 2005)	Telephone counselling	Current practice	Quality Adjusted Life Years	120.57	2.28	52.88	456	1437	5903	3885
(Feenstra et al. 2005)	(Minimal counselling + NRT)	Current practice	Quality Adjusted Life Years	128.66	1.77	72.69	319	1080	4548	2981
(Cornuz et al., 2006)	Bupropion	GP Counselling	Life Years Saved	64.52	1.6	40.33	340	1028	4163	2747
(Cornuz et al., 2006)	Nicotine inhaler	GP Counselling	Life Years Saved	828.85	1.65	502.33	-411	298	3530	2070
(Cornuz et al., 2006)	Nicotine patch	GP Counselling	Life Years Saved	116.4	1	116.40	137	567	2526	1641
(Cornuz et al., 2006)	Nicotine spray	GP Counselling	Life Years Saved	129.31	1	129.31	124	554	2513	1628
(Cornuz et al., 2006)	Nicotine gum	GP Counselling	Life Years Saved	147.65	1	147.65	105	535	2494	1609
(Stapleton et al., 1999)	Nicotine patch	Self-directed quit attempt	Life Years Saved	325.83	0.99	329.12	-75	350	2290	1414
(Feenstra et al. 2005)	(Intensive counselling + Bupropion)	Current practice	Quality Adjusted Life Years	177.18	0.89	199.08	48	431	2174	1387
(Feenstra et al. 2005)	(Intensive counselling + NRT)	Current practice	Quality Adjusted Life Years	218.35	0.74	295.07	-31	287	1737	1082

Table 4: Cost effectiveness estimates of smoking cessation programmes for developing countries (continued)

Study	Intervention	Comparator	Outcome measure	Incremental Cost (U.S Dollars)	Incremental Effect	ICER	INB for LICs (U.S Dollars)	INB for LMICs (U.S Dollars)	INB for UMICs (U.S Dollars)	INB for South Africa (U.S Dollars)
(Heitjan et al., 2008)	Bupropion	No Treatment	Life Years Saved	456.05	0.66	690.98	-289	-5	1288	704
(Heitjan et al., 2008)	Varenicline	Bupropion	Life Years Saved	456.05	0.66	690.98	-289	-5	1288	704
(Kaper et al. 2006)	Re-imbursement for SCT	No re-imbursement	Quality Adjusted Life Years	11.77	0.21	56.05	41	132	543	357
(Lal et al. 2014)	Proactive telephone counselling	Face to face counselling	Disability Adjusted Life Years	311.12	0.38	818.74	-215	-52	693	357
(Hall et al., 2005)	Bupropion	Placebo	Life Years Saved	163.54	0.29	563.93	-90	35	603	346
(Heitjan et al., 2008)	Varenicline	(Bupropion + Tailored therapy)	Life Years Saved	100.41	0.22	456.41	-45	50	481	286
(Tran et al., 2002)	Nicotine patch	Self-directed quit attempt	Life Years Saved	111.19	0.22	505.41	-56	39	470	275
(Tran et al., 2002)	Bupropion	Self-directed quit attempt	Life Years Saved	136.56	0.22	620.73	-81	14	445	250
(Tran et al., 2002)	Nicotine gum	Self-directed quit attempt	Life Years Saved	146.28	0.22	664.91	-91	4	435	240
(Boyd and Briggs 2009)	Group Counselling	Self-quit	Quality Adjusted Life Years	340.23	0.3	1134.10	-264	-135	452	187

Table 4: Cost effectiveness estimates of smoking cessation programmes for developing countries (continued)

Study	Intervention	Comparator	Outcome measure	Incremental Cost (U.S Dollars)	Incremental Effect	ICER	INB for LICs (U.S Dollars)	INB for LMICs (U.S Dollars)	INB for UMICs (U.S Dollars)	INB for South Africa (U.S Dollars)
(Boyd and Briggs 2009)	Pharmacy-based support	Self-quit	Quality Adjusted Life Years	162.94	0.18	905.22	-117	-40	313	153
(Wu et al. - 2014)	Computer-tailored self-help	Generic self-help	Quality Adjusted Life Years	6.96	0.006	1160.00	-5	-3	9	4
(Stanczyk et al. 2014)	Video-based computer - tailored intervention	General text-based advice	Quality Adjusted Life Years	10.08	0.001	10080.00	-10	-9	-7	-8
(Stanczyk et al. 2014)	Text-based computer-tailored intervention	General text-based advice	Quality Adjusted Life Years	84.66	-0.002	Dominated	-85	-86	-90	-88
(Cadier et al. 2016)	Full medical coverage of intervention	€50 coverage only	Life Years Saved	1010.09	0.13	7769.92	-977	-921	-667	-782
(Von Wartburg et al., 2014)	Varenicline	Bupropion	Quality Adjusted Life Years	23.26	-0.87	Dominated	-243	-617	-2322	-1552
(Von Wartburg et al., 2014)	Varenicline	NRT	Quality Adjusted Life Years	55.86	-0.95	Dominated	-296	-705	-2566	-1725
(Von Wartburg et al., 2014)	Varenicline	Unaided cessation	Quality Adjusted Life Years	62.5	-2.21	Dominated	-622	-1572	-5901	-3945

Figure 3: Incremental Net Benefit per intervention for LIC threshold

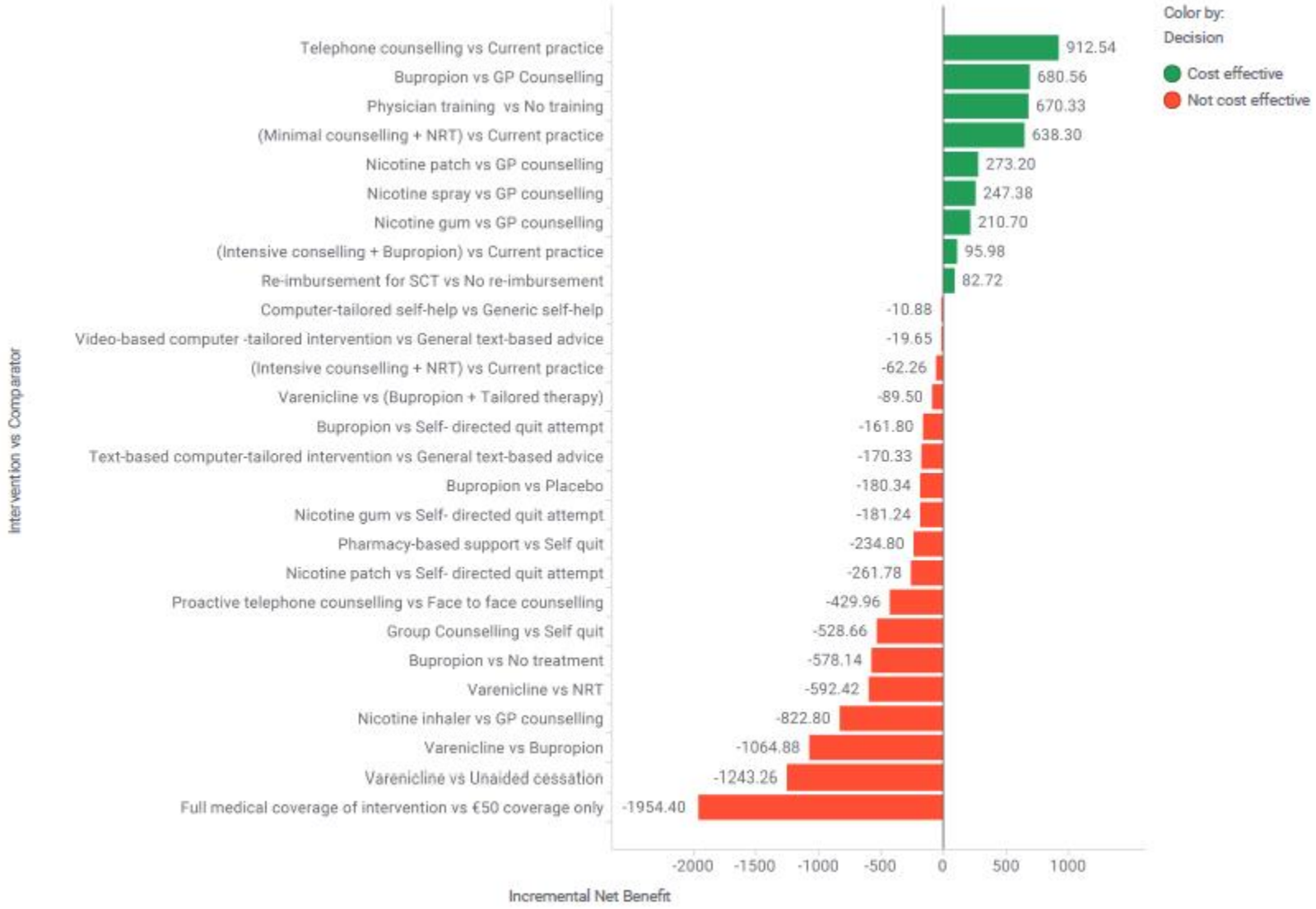


Figure 4: Incremental Net Benefit per intervention for LMIC threshold

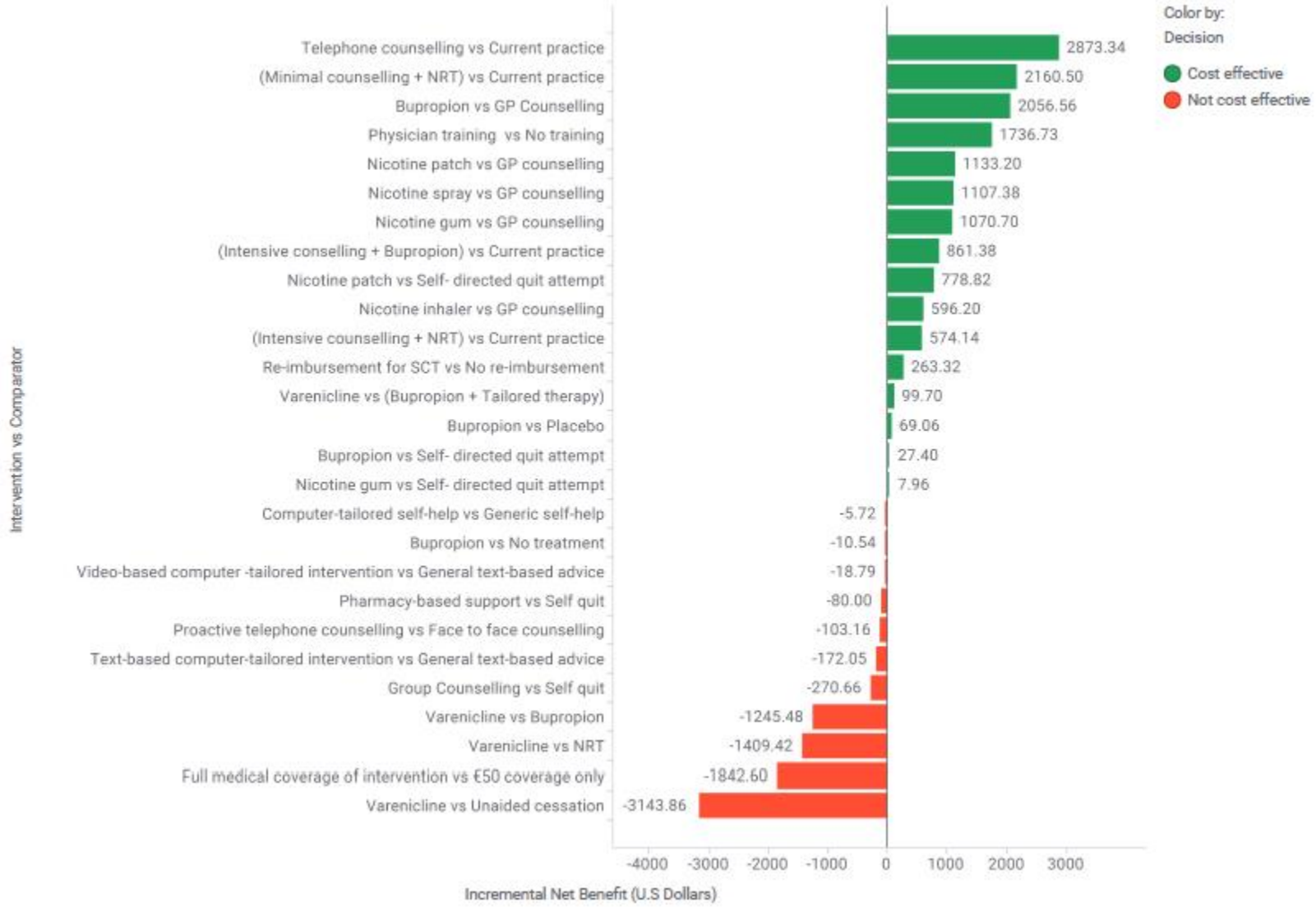


Figure 5: Incremental Net Benefit per intervention for UMIC threshold

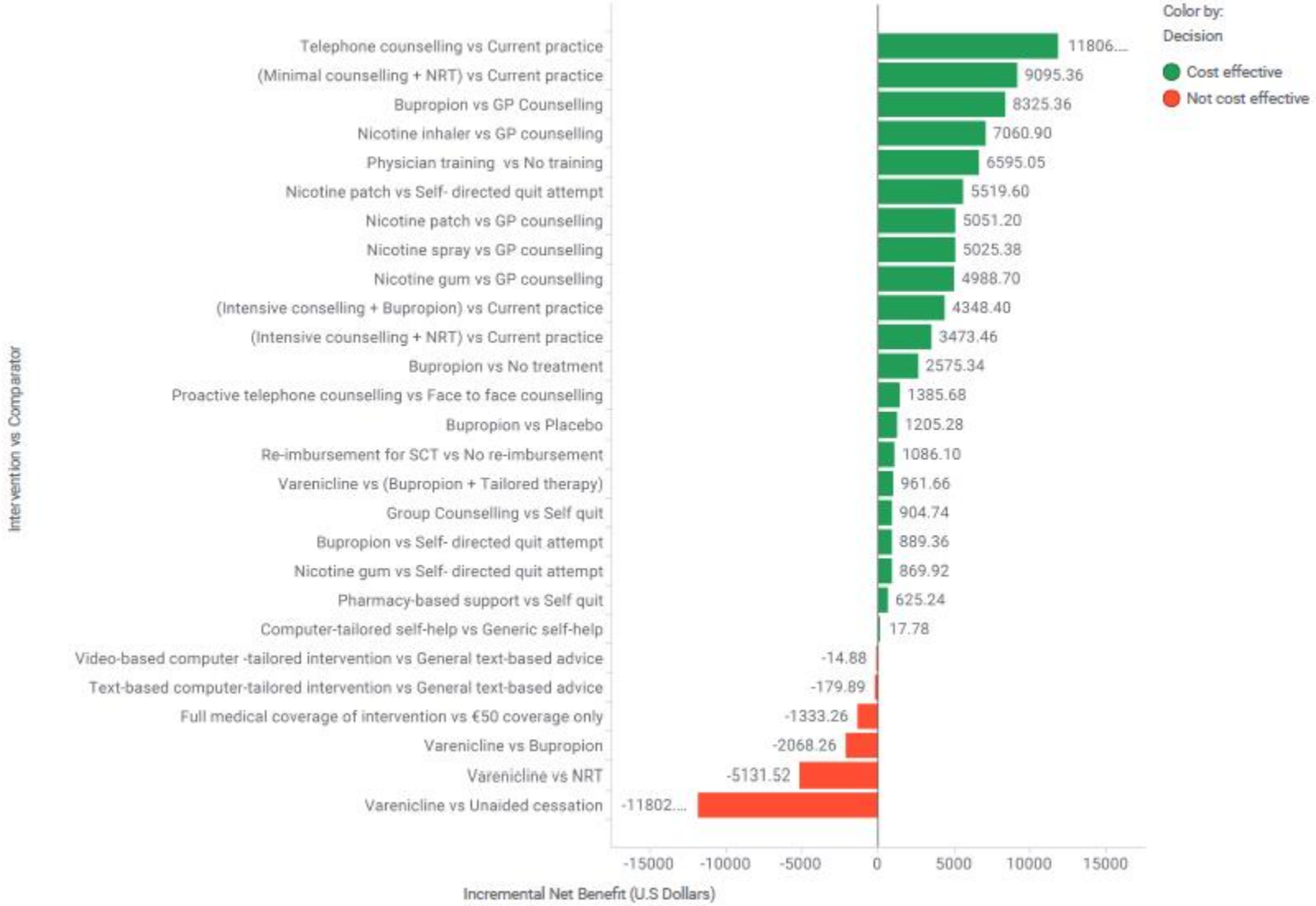
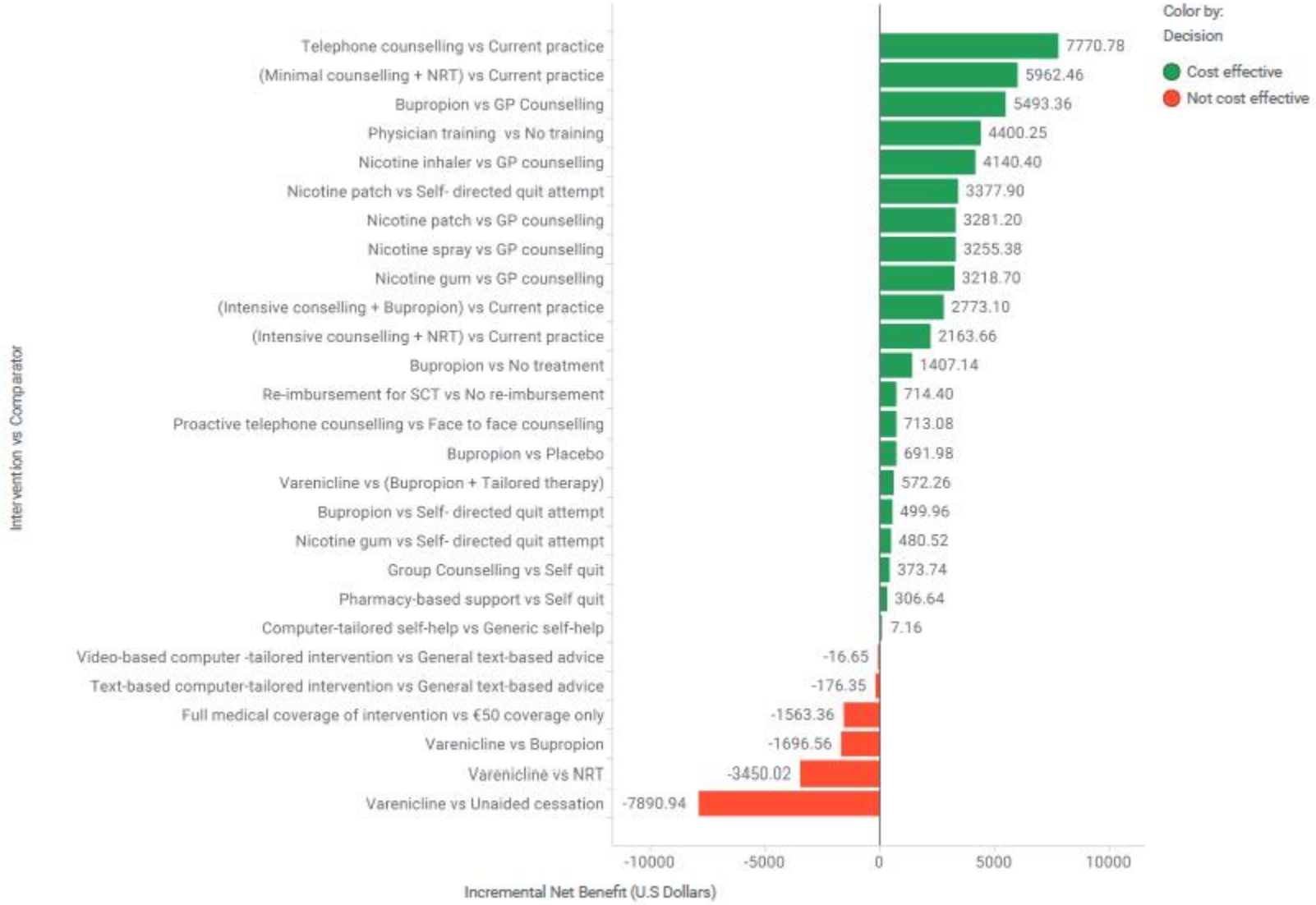


Figure 6: Incremental Net Benefit per intervention South Africa's threshold



Incremental net benefit analyses based on country-specific thresholds

Although Akers et al. (2007), López-Núñez et al. (2016) and Shearer & Shanahan, (2006) were all included in the narrative description of the review, INB estimates from these studies were not calculated since the authors reported quit rate and abstinence rate as health outcomes which are not ideal measures for valuing health benefits. It should be noted that quality of life measures (QALYs, LYG and DALYs) are the recommended health outcome measures for use when valuing health benefits (Stinnett & Mullahy, 1998) and thus INB estimates were only calculated for studies that reported such quality of life outcome measures.

This review also omitted INB analyses for primary country settings in which the primary studies were conducted since corresponding ICERs were already synthesized in the narrative description. INB estimates are summarized in table 4, visualized in figures (3-6) and subsequently discussed (in terms of least effective to most cost effective) based on willingness to pay thresholds for country settings in the following order: {a} low income countries {b} low-middle-income countries {c} upper middle-income countries and {d} South Africa. Detailed sub-group INB comparisons (nicotine-based, bupropion-based, varenicline-based and counselling-based interventions) were further made for South Africa.

Incremental net benefit based on LIC thresholds

Based on the LIC threshold, full medical coverage of smoking cessation treatment compared with partial coverage (€50) yields the lowest INB at -$977 while telephone counselling compared with current practice (mix of pharmacotherapies) yields the highest INB of $456. Overall, INB estimates for LIC country settings range from (in terms of lowest to highest): -$411 (nicotine inhaler compared with GP counselling) to $319 (NRT plus minimal counselling compared with a mix of other pharmacotherapies alone) for nicotine-based interventions, -$289 (bupropion compared with no treatment) to $340 (bupropion compared with GP counselling) for bupropion-based interventions, -$622 (varenicline compared with unaided cessation) to -$45 (varenicline compared with bupriopion plus tailored therapy) for varenicline-based interventions and lastly, -$264 (group counselling compared with self-quit) to $456 (telephone counselling compared with a mix of pharmacotherapies) for counselling-based interventions. While other

interventions may be relatively cost effective, varenicline appears non-cost effective at all for the LIC threshold.

Incremental net benefit based on LMIC thresholds

Varenicline compared with unaided cessation yields is the least INB estimate of -$1,572 based on the LMIC threshold. On the other hand, telephone counselling remains the most potential cost effective intervention even in LMIC settings when compared with current practice (mix of pharmacotherapies): INB of $1,437. Generally, INB estimates for LMIC country settings range from: $4 (nicotine gum compared with self-directed quit attempt) to $1,080 (NRT plus minimal counselling compared with a mix of other pharmacotherapies alone) for nicotine-based interventions, -$5 (bupropion compared with no treatment) to $1,028 (bupropion compared with GP counselling) for bupropion-based interventions, -$1,572 (varenicline compared with unaided cessation) to $50 (varenicline compared with bupriopion plus tailored therapy) for varenicline-based interventions and lastly, -$135 (group counselling compared with self-quit) to $1,437 (telephone counselling compared with mix of pharmacotherapies) for counselling-based interventions. Although some seem to yield low monetary benefits, all nicotine-based interventions appear cost effective for the case of LMIC settings.

Incremental net benefit based on UMIC thresholds

Varenicline compared with unaided cessation yields the lowest INB estimate of -$5,901 while telephone counselling compared with current practice (mix of pharmacotherapies) is the most cost effective with the highest monetary benefit of $5,903 based on the UMIC threshold. Overall, INB estimates for LMIC country settings range from: $435 (nicotine gum compared with self-directed quit attempt) to $4,548 (NRT plus minimal counselling compared with a mix of other pharmacotherapies alone) for nicotine-based interventions, $445 (bupropion compared with self-directed quit attempt) to $4,163 (bupropion compared with GP counselling) for bupropion-based interventions, -$5901 (varenicline compared with unaided cessation) to $1,288 (varenicline compared with bupriopion only) for varenicline-based interventions and lastly, -$90 (text-based computer-tailored counselling compared with general text-based advice) to $5,903 (telephone counselling compared with a mix of pharmacotherapies) for counselling-based interventions. In

this case, all nicotine-based and bupropion-based interventions seem potentially cost effective in UMIC settings.

Incremental net benefit based on South Africa's threshold

Based on South Africa's threshold, varenicline compared with unaided cessation yields the lowest INB of -$3,945 while telephone counselling compared with a mix of pharmacotherapies yields the highest cost effective INB of $3,885. In general, INB estimates for South Africa range from: $240 (nicotine gum compared with self-directed quit attempt) to $2,981 (NRT plus minimal counselling compared with a mix of other pharmacotherapies) for nicotine-based interventions, $250 (bupropion compared with self-directed quit attempt) to $2,747 (bupropion compared with GP counselling) for bupropion-based interventions, -$3,945 (varenicline compared with unaided cessation) to $704 (varenicline compared with bupriopion only) for varenicline-based interventions and lastly, -$88 (text-based computer-tailored counselling compared with general text-based advice) to $3,885 (telephone counselling compared with a mix of pharmacotherapies) for counselling-based interventions.

Although the broader literature suggests that low resource programmes (for example self-help materials) are generally more cost saving compared to programmes that are more resource intensive (for example nicotine replacement therapy), results in this review suggest that both programme types are relatively cost effective in South Africa's setting. For example, all nicotine-based, bupropion and telephone counselling programmes seem to be potentially cost effective for South Africa's threshold.

In contrast, varenicline only seems cost effective when compared with bupropion for which it still yields a lower INB estimate of $57 relative to other interventions. But compared with NRT and unaided cessation, varenicline seems non-cost effective. Moreover, INB estimates calculated from (von Wartburg et al., 2014) also suggest that varenicline may be non-cost effective even when compared with bupropion: INB of -$1,552 based on South Africa's threshold.

In particular, results calculated from (Stapleton et al., 1999) and (Tran et al., 2002) suggest that nicotine-based interventions may be cost effective when compared with self-directed quit

attempt: $2,290 for nicotine patch and $240 for nicotine gum respectively. Adding NRT to physician counselling yields cost effective INB estimates of: $2,981 when added to minimal counselling and $1,082 when added with intensive counselling compared with current practice (mix of other pharmacotherapies) based on calculations from (Feenstra et al., 2005).

Nicotine patch also yields a cost effective INB estimate of $1,641 compared with GP counselling based on calculations from (Cornuz et al., 2006). Similarly, both nicotine spray and nicotine inhaler may be cost effective in South Africa's setting with relatively high monetary benefits: $1,628 and $2,070 respectively. .

INB estimates calculated from (Hall et al., 2005) and (Heitjan et al., 2008) suggest that bupropion is cost effective: $346 and $704 for bupropion compared with a placebo respectively. Data from (Cornuz et al., 2006) and (Tran et al., 2002) also shows that bupropion is cost effective: INB estimates of $2,747 (bupropion compared with GP counselling) and $250 (bupropion compared with self- directed quit attempt) respectively. Likewise, INB calculations from (Feenstra et al., 2005) suggest that adding bupropion to physician counselling programmes may be cost effective since it yields an INB of $1,387 compared with a mix of other pharmacotherapy-based interventions. Therefore, all bupropion programmes seem relatively cost effective for South Africa's threshold.

For counselling-based interventions, telephone counselling programmes appear relatively more cost effective when compared with pharmacotherapy-based and face to face counselling programmes. That is to say, INB estimates obtained using data from (Feenstra et al., 2005) and (Lal et al., 2014) suggest that telephone counselling yields the highest monetary benefit of $3,885 when compared with a mix of pharmacotherapy-based interventions and $357 when compared with face to face counselling respectively. Group counselling also appears cost effective with an INB estimate of $187 compared with self-directed quit attempt based on calculations from (Boyd & Briggs, 2009).

Finally, findings suggest that computer tailored interventions may yield low monetary benefits in South Africa's setting. That is to say; both text-based and video-based computer tailored

interventions yield non-cost effective INB estimates of -$88 and -$8 compared with general advice (self-help manuals only) based on data obtained from (Stanczyk et al., 2014) respectively. However, INB estimates calculated using data from (Wu et al., 2014) show that computer-tailored self-help may be cost effective when compared with generic self-help (self-help manuals only), although it yields relatively very low monetary benefits of $4 based on South Africa's threshold.

5.0 Discussion

This study reviewed several primary studies and explored the potential cost effectiveness of smoking cessation programmes in developing countries using the INB approach. The analysis exclusively focuses on smoking cessation programmes rather than other smoking related interventions like policy-based tobacco control programmes. The trend in results highlights that incremental net benefit estimates may be lower in developing countries due to low income thresholds. This may imply that majority of these programmes would yield relatively low monetary benefits if implemented in developing countries. Moreover, several interventions tailored for developed country contexts may not be economically feasible in low income country settings. Nevertheless, some smoking cessation interventions may potentially be cost effective in middle income country settings and South Africa although they generally yield low monetary benefits unlike developed countries where higher monetary benefits are witnessed.

Overall, pharmacotherapy particularly bupropion, varenicline and nicotine-based interventions seem relatively expensive in developing country settings although the broader literature suggests that they are highly effective (yield high health benefits) compared to low resource behavioural interventions (self-help and counselling based programmes). On the other hand, unaided cessation and behavioural therapy-based interventions seem to be less expensive and more economically feasible for low- and middle income countries although they yield lower health benefits and cessation rates relative to pharmacotherapies.

Currently, average generic prices per dosage (adapted from South Africa medicine price registry-https://mpr.code4sa.org/) show that bupropion ($39), varenicline ($45) and nicotine gum ($18) in South Africa cost relatively higher or equal to prices in the United States (adapted from www.goodrx.com): bupropion ($31), varenicline ($49) and nicotine gum ($10) respectively.

Moreover, prices for the nicotine patch in other developing countries (Brazil, Chile, Puerto Rico, and Uruguay) are generally higher than in the USA, and at least three times higher than prices in South Africa (Gilbert et al. 2004).

It is therefore important to note that while decision makers in developing country settings may consider implementing smoking cessation interventions, affordability of these programmes will be the major deciding factor of their feasibility. Therefore, developing countries may only benefit if smoking cessation interventions become widely available at relatively lower costs in these resource constrained country settings. A solution to this is resorting to local production of pharmacotherapy drugs by local manufacturers. Adoption of this strategy by local manufacturers in India effected a significant reduction in generic pharmaceutical prices for bupropion and nicotine gum by 12.5% of the U.S price (Gilbert et al., 2004).

However, adopting local production of smoking cessation pharmacotherapies may be a challenge to some developing countries due to the licensing, infrastructure capacity, capital investment and more generally, technology requirements associated with such large-scale investments (Gilbert et al. 2004). This probably explains the wide use of media campaigns and policy-based (taxation and regulation) interventions rather than pharmacotherapy-based and behavioral-based cessation interventions in developing country settings. In South Africa, media campaigns and quit-lines are popular smoking cessation interventions although their cost effectiveness is still unknown.

Whilst some interventions may appear economically feasible in developing country settings, the high variation in studies makes it difficult to make conclusive judgement about their cost-effectiveness. This is because countries have different health care systems and service delivery systems. Additionally, costs are measured from different perspectives. It would therefore be better if each country had specific CEA data, but it is not possible for every country to conduct cost effectiveness analyses due to lack of resources.

Moreover, some countries have geographical, demographical and epidemiological differences and the CEA results may even be different from region to region; making it difficult to conduct investigations within these countries. Despite these situations, there is need for policy makers to

use CEA results from other countries and apply them to their own setting, although it may not be practical and less credible. This necessitates the need for using the INB approach and the WHO-CHOICE country thresholds to measure cost effectiveness of interventions as seen in this review. These thresholds link per capita GDP with returns on investments in health to define the characteristics of a cost–effective and a very cost–effective intervention (Marseille et al., 2014). However, use of these criteria has some major shortcomings.

The first limitation is that interventions considered cost effective based on the WHO-CHOICE criteria may still not represent the best use of a country's health budget. That is to say, it is not enough to know that per given outcome, an intervention costs less than three times the local annual per capita gross national income. Moreover, two interventions may all appear cost effective given that they yield an ICER which is below the WHO-CHOICE thresholds. However, this review applies the WHO-CHOICE criteria together with the INB approach which clearly ranks the cost effectiveness of interventions since the programme that yields the highest monetary benefit represents the best value for money.

Secondly, the WHO-CHOICE thresholds do not determine whether its assumptions explicitly represent individual willingness to pay for healthcare. When using these thresholds, it is assumed that individuals are willing to pay the equivalent of three times less their annual per capita income per disability life year averted (Hutubessy et al., 2003). However, the value people attach to a healthy life extends beyond income dimensions (Shillcutt et al., 2009). In addition, these thresholds may not put into consideration the society's willingness to pay for healthcare and thus may misrepresent the cost effectiveness of a programme from the societal perspective.

Therefore, these thresholds should not be considered alone while making allocation decisions. Affordability, feasibility and other country specific decision rules should also be considered to determine which intervention yields the best value for money. Never the less, this approach remains the most widely recommended alternative by the World Health Organization's Commission on Macroeconomics and Health (World Health Organization, 2001).

Despite the findings of this review, the included studies are also subject to several methodological limitations. Firstly, differences in methods and inputs used to estimate costs led to wide variation in the study outcomes and results. Whilst the guidelines for costing in cost-effectiveness studies remain unclear, some studies did not report standard cost measures (https://www.hsph.harvard.edu/hcra/) as recommended by the Harvard Centre for risk analysis and the panel for cost-effectiveness in health. That is to say, some studies limited the cost components to only direct costs of treatment while other studies included both indirect costs and direct costs associated with the programme.

For example, two studies evaluated the cost-effectiveness of varenicline: one primary CEA limited its cost components to only direct healthcare costs of varenicline while another economic evaluation included genetic testing costs for relapse in addition to direct costs of varenicline treatment. As a result, both studies suggest different findings: varenicline is cost-effective in the USA (Heitjan et al. 2008) and non-cost-effective in Canada (von Wartburg, Raymond, and Paradis 2014) compared with bupropion. On comparing cost components, it appears that including genetic testing costs in one study increased the total programme costs thus creating variation in findings for the same intervention.

Second, some studies estimated costs based on assumptions that may misrepresent the true costs of the intervention. For example, Tran et al. (2002) and von Wartburg et al. (2014) assumed zero costs for the unaided smoking-cessation programme since it requires neither the administration of a drug nor a physician visit. But this may not be the case since smokers who attempt to quit may incur non-medical costs (cost to caregivers, cost of obtaining self–help manuals for smoking-cessation and expenses of attending smoking-cessation campaigns). Thus, the true cost estimates for unaided smoking cessation may be underestimated.

Several study designs were used to measure health outcomes including randomized control trials, observational study or decision analytic models. If participants are a selection of motivated smokers, cessation rates are likely to increase. For this reason, cost-effectiveness estimates may be biased. Moreover, Feenstra et al. (2005) acknowledged that cost-effectiveness estimates

obtained from clinical trials tend to be higher than those from modelling study designs because participants are mostly a selection of volunteers who were willing to quit.

Some cost effectiveness analyses were conducted in strictly monitored settings (RCTs). Such study settings may differ from "real life" healthcare systems in terms of patient's adherence to treatment, characteristics and levels of supervision (Jones et al. 2019). Therefore, strictly supervised clinical trials are more likely to yield higher health benefits compared to those that are less monitored. These factors may cause bias in results which also causes variation in costs and health outcomes of the evidence presented. Also, studies conducted in controlled settings follow a strict eligibility criterion which limits the diversity of study participants. Thus, the evidence presented may not apply to all populations.

Furthermore, using placebos as comparators may limit the validity of the evidence (M. F. Drummond et al. 2015). By nature, cost effectiveness analyses aim to measure the costs and effects between interventions on an incremental basis. In contrast, placebos barely yield any treatment effect thus estimating opportunity costs and incremental effectiveness is limited with such controls (Sun et al., 2010).

In contrast to some cost-effectiveness analyses, avoidable costs from diseases that may arise due to smoking (cardiovascular diseases, lung cancer, and respiratory diseases) are not accounted for. Cessation programmes that prevent smoking related diseases yield future cost-savings and utility through added life years gained (Nyman, 2004). An ideal CEA should discount for such future cost-savings. However, several analyses included in the review did not account for such cost benefits. Therefore, cost-effectiveness of programmes may be underestimated. Nevertheless, whether there is a direct relationship between cost savings from avoidable smoking related diseases and utility gained remains a discussion beyond the scope of this review.

For a far-reaching conclusion of evidence, measuring the cost effectiveness of programmes over long-term horizons (more than 18 months) allows for capturing economically and clinically important outcomes (López-Núñez et al., 2016). In contrast, several studies included in this review were not conducted beyond short-term (12 weeks to 52 weeks follow up) horizons. For

this reason, incremental monetary benefit may be underestimated since cost–savings may occur beyond short-term horizons. Moreover, use of short-term analyses to assess long-term economic and patient outcomes may limit the validity of cost effectiveness outcomes (Sun et al., 2010).

Studies reviewed also mainly focused on cessation therapies and programmes; including first-line pharmacotherapy-based and behavioural–based interventions. Thus other important policy interventions, such as price and tax increases, media campaigns, smoke free air laws and workplace smoking interventions were not included. This review would have benefited from considering both tobacco control and cessation programmes for purpose of guiding policy in developing country settings.

While this review aimed to provide insights of whether smoking cessation programmes are cost effective in developing country settings or not, findings cannot be completely transferred or applied in these settings without considering transferability. Therefore, "a leap of faith is always required when applying any study findings to the population at large. In making that jump, one must always strike a balance between making justifiable broad generalizations and being too conservative in one's conclusions" (Friedman et al., 1985, p. 285).

However, due to the following factors, transferability of these results may be limited. Mainly, differences in cost and resource components across countries may limit the applicability of the cost-effectiveness results presented in this review. Moreover, all the studies included in the review were conducted in high-income country settings (United States, United Kingdom, Netherlands, France, Australia, Hungary and Switzerland) for which health technologies and systems are advanced. Unlike high income countries, healthcare systems and clinical practice in low- and middle-income country settings are limited in terms of technology. For this reason, evidence presented in this review may not directly apply to low- and middle-income country settings.

Variation in discount rates for effectiveness of interventions may also limit the transferability of the evidence presented. Discounting influences cost-effectiveness measures since it allows for adjustment of future incremental costs and benefits to current value associated with an

intervention. Therefore, using a lower (higher) discount rate in one country may underestimate (overestimate) cost-effectiveness decisions for different country settings. The U.S Panel on Cost-Effectiveness in Health and Medicine suggests a 3% discount rate for cost and benefit outcomes (Weinstein et al., 1996). However, discount rates vary across countries: 4% for the Netherlands (Hoogendoorn et al., 2008), 5% for both Canada and Germany (von Wartburg et al., 2014). Moreover, the UK has different discount rates for both costs (3.5%) and effects (1.5%) (Towse & Pritchard, 2002).

In addition to the above broader aspect issues, the target population characteristics may influence the cost-effectiveness of interventions. These may include: sex, age, race, co-morbidity, disease incidence. For example, (Lal et al. 2014) found that patients aged 20-35 years respond quicker to cessation treatment than older patients. Thus, cost-effectiveness analyses conducted in a younger population may not be applicable to settings with older age groups.

Variation in monitoring, patient compliance and patient preference may also limit the applicability and generalizability of these findings to developing country contexts. The effectiveness of a smoking-cessation programme may depend on strict monitoring, patient compliance, value and preference for health. Patients in closely monitored pharmacotherapy treatment groups are more likely to benefit from a cessation programme than others. This may make a programme appear cost-effective. In addition, programmes were participants have high compliance and motivation for quitting are more likely to yield higher benefits due to high cessation rates compared to programmes with less-compliant participants.

Absence of some smoking-cessation interventions and health monitoring technologies in some low-income country settings may also limit applicability of the evidence presented. It should be noted that some pharmacotherapy-based and behavioral-based smoking cessation interventions are not popular or even do not exist in some developing country settings. Thus, applying these findings in such settings may only be hypothetical which may significantly differ from the actual feasibility if interventions were adopted.

Despite the limitations mentioned, Antonanzas et al. (2009) and Boulenger et al. (2005) developed indices that measure generalizability and specific transferability of the cost-effectiveness results. Further research can benefit from applying these standardized transferability indices to assess the generalizability and applicability of the results presented in other country settings.

Overall, this review has several limitations. First, a comprehensive review should be conducted in a systematic manner as recommended in the Cochrane handbook for systematic reviews (Higgins & Green, 2011). In contrast, this review was not conducted in strict accordance to the guidelines of a systematic review; did not conduct a systematic literature search of all available databases, did not perform a quality assessment of the studies, and data were extracted and coded by one individual only. Thus, the reliability of the results is limited. However, time and resource constraints precluded a fully-fledged systematic review.

Secondly, only published studies from selected databases were included. This may have excluded relevant unpublished studies. In fact, inclusion criteria were limited to cost-effectiveness analyses, thus potentially relevant studies might have been excluded. As a result, the body of evidence (18 studies) presented may not allow for a robust conclusion regarding cost-effectiveness of smoking-cessation programmes.

Third, all studies included in this review were conducted in developed country contexts. For this reason, transferability and applicability of the evidence should be considered. However, this review did not measure the degree of transferability of these results due to time limitations. Moreover, applicability of the evidence may be dependent on the specific economic and population characteristics of a given health care setting. Further research can apply standardized transferability indices to the studies reported in this narrative synthesis.

Several studies used quit rates as a metric for effectiveness. Despite being a common measure of health outcomes, quit rates do not capture “healthy years” gained or saved. Thus, they are not the best metric for measuring health benefits in cost effectiveness analyses. In contrast, QALYs, life adjusted years saved and DALYs are the most recognized metrics for measuring health benefits

(M. F. Drummond et al. 2015). Therefore, reliability of results from studies that used quit rates as a measure for effectiveness is limited.

Furthermore, pooling of cost-effectiveness results in a meta-analysis would potentially improve the validity of the evidence presented. However, statistical methods for pooling cost-effectiveness outcomes are limited. Moreover, variation among the cost components, study designs, outcome measures and interventions limited the ability to conduct a meta-analysis and compare studies directly. Additional differences in methodology, study assumptions, price estimates, time horizons and population settings limit the ability to draw direct conclusions about the study findings.

Finally, using the incremental net benefit as a yardstick for determining cost-effectiveness of programmes limits the validity of results presented. However, the overlapping weaknesses of the alternative ICER approach make the INB approach more appropriate for determining the cost effectiveness of smoking cessation interventions. A more detailed argument in favour of the INB approach can be seen in (Willan, 2004).

6.0 Conclusion

In sum, drawing conclusions about the cost effectiveness of smoking-cessation programmes may entail making trade-offs between the estimated net benefits and costs. However, making such trade-offs goes beyond the evidence demonstrated in this review and thus requires additional information that is specific to the characteristics of given country settings. Nevertheless, findings suggest that telephone counselling and pharmacotherapy-based interventions potentially yield higher health and monetary benefits when compared with low resource intensive programmes like self-help manuals; although pharmacotherapies appear relatively costly in low income country settings. This review highlights several shortcomings in methodology and transferability of the results. Efforts to improve statistical methods for pooling, comparing and transferability of cost-effectiveness outcomes will make future studies more robust and applicable to “real life” settings.

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