Optimizing Delivery of Health Care Interventions (ODHIN)

Cost-Effectiveness – Analysis of the WP5 Trial

Addendum to Deliverable D3.1, Work Package 3

Colin Angus

Jinshuo Li

Steve Parrott

Alan Brennan

December 2014

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Acknowledgements

The authors would like to thank all of the collaborating partners within the ODHIN project for their input into WP3. In particular we would like to thank Peter Anderson for his assistance with the trial analysis presented herein, and the WP3 partners who assisted with the development of the country-specific models reported in D3.1 and used extensively in the present analysis – Emanuele Scafato, Silvia Ghirini, Aleksandra Torbica, Francesca Ferre, Pierluigi Struzzo, Myrna Keurhorst, Miranda Laurant, Luiza Słodownik, Katarzyna Okulicz-Kozaryn and Krzysztof Brzózka.

The research leading to these results or outcomes has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 259268 – Optimizing delivery of health care intervention (ODHIN). Participant organisations in ODHIN can be seen at: www.odhinproject.eu. The views expressed are those of the authors and not necessarily those of the European Commission.

1 INTRODUCTION

The main objectives of ODHIN's Work Package 3 were:

1) To adapt the Sheffield Alcohol Policy Model and its appraisal of the cost-effectiveness of screening and brief interventions from its current England context, to model the effectiveness of screening and brief interventions in the Netherlands, Poland and Italy
2) To use the results of the modelling to consider generalizability of interventions across the EU
3) To investigate modelling long-term cost-effectiveness of dissemination approaches studied in RCTs in other WPs

The results of the work relating to objectives 1 and 2 was presented in deliverable D3.1 (Angus et al. 2013). This addendum presents the results of the work relating to objective 3. **A summary of the key findings of this WP, incorporating both D3.1 and this addendum can be found in Section 5.**

2 METHODS

2.1 WP5 Trial Design

The ODHIN trial was undertaken in 120 primary health care units (PHCU) equally distributed across 5 countries (England, Netherlands, Poland, Catalonia and Sweden) (Keurhorst et al. 2013). The trial examined the impact of 3 alternative strategies for improving the uptake of Screening and Brief Intervention (SBI) delivery in primary care – Training and Support (TS), Financial Reimbursement (FR) and Referral to an Online Brief Intervention (eBI) – both individually and in combination using a factorial design to give 8 strategies in total (Control, TS, FR, eBI, TS+FR, TS+eBI, FR+eBI and TS&FR&eBI). Randomisation was undertaken at the practice level, with 3 practices in each country allocated to each of the 8 strategies.

2.2 Trial outcomes data

The trial collected data on three key performance measures of SBI delivery:

1) The screening rate – the proportion of eligible patients who were screened for heavy drinking using the AUDIT-C screening tool[1]
2) The screen positive rate – Screen positives were defined in Catalonia and England as men and women who scored ≥5 on AUDIT-C, and in Poland, Netherlands and Sweden as men who scored ≥5 and women who scored ≥4 on AUDIT-C.
3) The Brief Intervention rate – the proportion of patients who screened positive on AUDIT-C who subsequently received a Brief Intervention

Data was collected within the trial at 3 time points – at baseline (i.e. pre-intervention), during a 12 week implementation period at which time the strategies were being implemented, and during a 4-week follow-up period 6-months later (i.e. post-intervention).

2.3 Intervention Costs during the Trial

For each of the 5 countries in the trial, data on the costs associated with each strategy was collected during the trial period by the local teams responsible for administering the trial. These costs included, where appropriate:

- The cost of printing literature

[1] A small number of patients in Catalonia were screened using an alternative screening tool, ALRIS, although practitioners were encouraged to use AUDIT-C wherever possible.

- The direct cost of delivering training and support to practitioners (including trainers' time and venue costs)
- The direct cost of introducing practitioners to the eBI referral system
- The costs of practitioners' time away from patients whilst receiving this training, including time travelling to and from the venue where training was provided

Any costs which were specific to organising the trial itself were excluded (such as the cost of printing the tally sheets used to record practitioners' SBI activity).

In addition to this data, estimates were collected within each country from a subsample of participating practitioners of the estimated average duration of a Brief Intervention and the average time taken to introduce a patient to the eBI tool. Estimates of the per-minute cost of practitioners' time were also obtained together with full details of the structure of the financial incentives offered to participants in FR arms of the trial (as each country was at liberty to set their own incentive structure provided they did not exceed the allocated budget for incentives within the trial).

Estimates were also collected of the total number of practices and providers within each country in order to calculate estimates of full roll-out cost at the national level of each intervention.

2.4 Cost-effectiveness modelling using the Sheffield Alcohol Policy Model (SAPM)

The Sheffield Alcohol Policy Model (SAPM) is a causal epidemiological model which has previously been used to appraise pricing and SBI policies in England (Purshouse et al. 2013; Purshouse et al. 2009) As part of the ODHIN project, this model was adapted to appraise the cost-effectiveness of SBI policies in primary care in Italy, the Netherlands and Poland.

The model synthesises published evidence and country specific data on:

- Baseline patterns of self-reported alcohol consumption in the population by age and gender subgroups
- Baseline mortality and hospitalisation rates for 48 different alcohol-related health conditions by age and gender subgroups
- Frequency of primary care attendance by age and gender subgroup
- Costs of primary care practitioners and the costs to health services of alcohol-related illness
- Health-related quality of life data for all 48 different alcohol-related health conditions and the general population by age and gender.

And uses these inputs to calculate

- The number of people who would receive a brief intervention over a 10 year time horizon
- The resulting reductions in alcohol consumption
- The consequent reductions in mortality, hospitalisation and in healthcare costs
- And hence the incremental cost per quality adjusted life year gained by the strategy of screening versus no screening

The results of these 4 country (England, Italy, the Netherlands and Poland) models were then used to develop a generalised meta-model for the whole of Europe, which estimates the cost-effectiveness of SBI programmes from 6 key factors. Full details of these models and the corresponding results can be found in D3.1. For the analysis of the ODHIN trial results, these country-specific models were used for England, the Netherlands and Poland. As full country-specific models were not available for Catalonia and Sweden, results for these countries were analysed using the meta-model.

2.5 Analysis of trial outcomes

For each of the 5 countries participating in the ODHIN RCT, the baseline screening rate (Eq1), screen positive rate (Eq2) and brief intervention rate (Eq3) were calculated by pooling the baseline data from all practices (as all practices were blind to their allocation to a strategy at this stage). These baseline rates are shown in Table 1.

Equation 1:

$$Screening\ rate = \frac{Total\ no.of\ eligible\ consultations\ in\ which\ patient\ was\ screened}{Total\ no.of\ eligible\ consultations}$$

Equation 2:

$$Screen\ positive\ rate = \frac{Total\ no.of\ patients\ screening\ positive}{Total\ no.of\ patients\ screened}$$

Equation 3:

$$Brief\ Intervention\ rate = \frac{Total\ no.of\ patients\ receiving\ a\ BI}{Total\ no.of\ patients\ screening\ positive}$$

Table 1 – Baseline SBI measures by country

Country	Screening rate	Screen positive rate	Brief Intervention rate
Catalonia	6.8%	5.0%	48.3%
England	4.6%	48.9%	85.9%
Netherlands	5.3%	44.4%	70.4%
Poland	2.0%	41.2%	95.8%
Sweden	10.6%	29.4%	74.0%

Statistical analysis of the impact of each of the 8 strategies was conducted by the WP5 team in accordance with the analysis plan laid out in the trial protocol (Keurhorst et al. 2013). This analysis takes advantage of the trial's factorial design to compare the outcomes in, for example, all arms which include a TS component, to all those which do not, thus isolating the effect of Training and Support whilst improving the statistical power of the calculations over a simple comparison between the 8 strategies. Combination strategies are dealt with in the same way (e.g. all arms including TS and FR are compared to all arms which do not include both components). Statistical models were fitted separately for each outcome at each time point (implementation and follow-up). Mixed Analysis of Variance (ANOVA) models were fitted using SPSS Version 22 (IBM Corp.) using the MIXED command, to estimate the marginal mean outcome rate for each factor at each time point, controlling for baseline outcome rates and accounting for the hierarchical structure of the data, with practices nested within countries. From these marginal means, the percentage change in each outcome from baseline to each time point was calculated. These changes are presented in Table 2.

The main results of interest are those for the implementation period. These suggest that for screening rates, both TS and FR increase the screening rate and indeed the combination strategy TS+FR has the highest effectiveness at increasing screening rates. Perhaps surprisingly, all interventions decrease the screen positive rate except eBI although the scale of these reductions is relatively modest. The BI rates are already at a high baseline level (see Table 1), however all

strategies increase BI rates (although the increase in the control arm is negligible). TS alone, TS+FR and TS+FR+eBI appear to have the highest effects on increasing the BI rates.

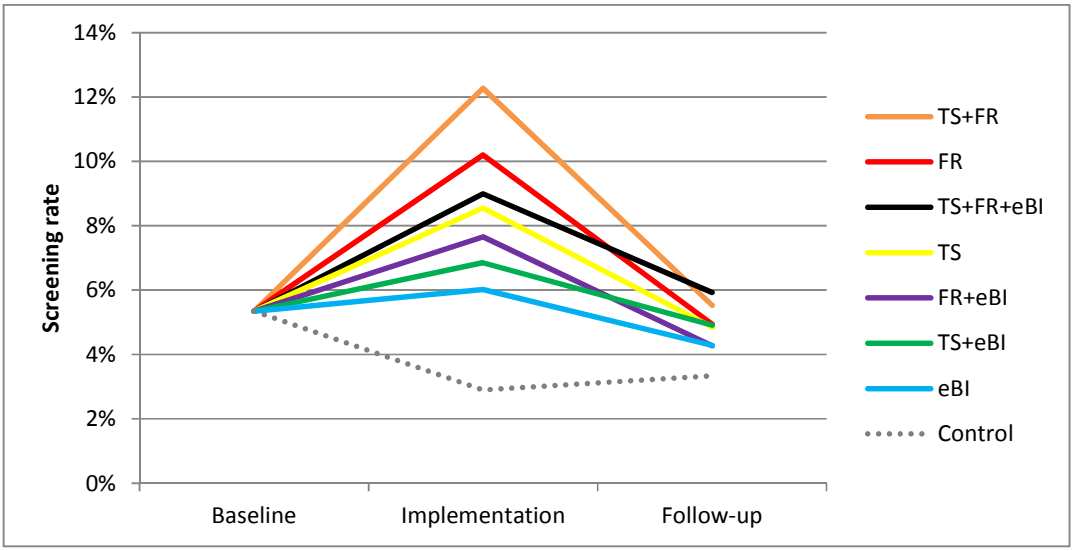
When the interventions are withdrawn (baseline to follow up columns) the effects of most interventions on these three outcome measures tend to be somewhat reduced. In many cases the rates fall back even further to below those at baseline e.g. removal of the FR seems to cause the screening rate to fall. Interestingly, whilst screening and positive screen rates decrease at follow-up for almost all strategies, BI rates remain above baseline levels for all strategies except for control.

Table 2 - Impact of implementation strategies on trial outcomes

Strategy	Baseline to implementation			Baseline to follow-up		
	Change in screening rate	Change in screen positive rate	Change in BI rate	Change in screening rate	Change in screen positive rate	Change in BI rate
Control	-45.8%	-7.1%	0.2%	-37.5%	-8.4%	-22.1%
TS	59.8%	-7.4%	21.2%	-9.5%	-17.6%	7.5%
FR	90.7%	-12.5%	18.2%	-7.6%	-16.8%	3.8%
eBI	12.5%	3.8%	14.0%	-20.0%	-1.4%	1.2%
TS+FR	129.5%	-15.8%	24.8%	3.2%	-27.8%	10.0%
TS+eBI	28.0%	-4.0%	17.8%	-8.3%	-18.7%	3.1%
FR+eBI	43.1%	-6.3%	14.9%	-20.1%	-13.4%	3.8%
TS+FR+eBI	68.2%	-20.6%	22.9%	10.7%	-35.3%	4.4%

The changes shown in Table 2 are applied to the country-specific baseline rates shown in Table 1 in order to calculate the screening, screen positive and BI rate for each country during implementation and at follow-up under each strategy. For a small number of country/strategy combinations, the implied BI rate at implementation was greater than 100%, in which cases the number was capped at 100%. Figure 1 illustrates these results for screening rates for Catalonia.

Figure 1 - Change in screening rates in the trial in Catalonia



2.6 Adapting trial outcomes to SAPM

The trial results presented in Table 2 tell us about the impact of the trialled strategies on SBI delivery to patients presenting to primary care over a 12-week implementation period and a subsequent 4-week follow-up period 6 months later. The Sheffield Alcohol Policy Model, however, simulates 10 years of implementation in discrete annual cycles and the trial results must therefore be converted to account for this longer duration. It is also necessary to account for the fact that the frequency of family doctor visits varies between population subgroups.

This conversion is performed using detailed data on primary care consultation frequencies over 5 years in the Netherlands (obtained from the Netherlands Information Network of General Practice (LINH)) in combination with the best available data on population consultation frequencies for each of the 4 other countries. Briefly, country-specific data on the proportion of each age-gender subgroup of the population who would be screened in each year if the screening rate was 100% are adjusted using a model constructed from the LINH data which accounts for the differential probability across the population of visiting a family doctor at all in each year of the modelled programme, together with the variation in annual frequency of consultations for those who do visit their doctor over the course of the year, as well as accounting for the screening rates observed in the trial.

A key challenge in extending the estimated effect of each strategy from the 6-month trial period to a 10-year implementation is the fact that, whilst Training & Support and eBI strategies are essentially 'one-off' policies, in the sense that practitioners are trained or introduced to the eBI tool at the outset and not subsequently re-trained, Financial Reimbursement is an ongoing process. The follow-up measures are therefore not directly comparable across all strategies as practices allocated to TS and eBI strategies were essentially still under implementation conditions (e.g. practitioners could still refer patients to the eBI tool), whilst those allocated to FR strategies were not under implementation conditions, as no further payments were made after the 12-week implementation period. In order to overcome this issue, two separate analyses were conducted.

The 'within-trial analysis' models exactly what was implemented in the trial (i.e. FR withdrawn after 12 weeks) and assumes that the rates observed at follow-up would be sustained in the long term.

The 'full implementation analysis' models FR payments continuing for the full 10 years and assumes that the trial outcomes observed during the implementation period are maintained in the long term. As a sensitivity analysis within the full implementation analysis, we also examine the impact of assuming that training must be re-delivered every 5, or every 2, years in order to achieve this persistence of effect.

The results of this process for each analysis are the estimated proportion of the population of each age-gender group who are screened in each year over 10 years of policy implementation, for each country and strategy combination.

For each individual screened, the probability that they screened positive is estimated from a logistic regression, with parameters calibrated to match the proportion of positive screens observed in the trial data. For details of this regression and calibration process please see Appendix B.

Finally, the BI rate from the trial data is applied to estimate the proportion of individuals who screened positive that will subsequently receive an intervention. The average consumption reduction of 12.3% taken from the latest Cochrane meta-analysis (Kaner et al. 2007), is assumed for all individuals who receive a BI. This reduction is assumed to decay linearly back to age-adjusted pre-intervention consumption levels over the following 7 years, based on evidence from the work of Fleming and colleagues' (Fleming et al. 2002). For the simplicity of the model, it is assumed that no

individuals are screened more than once over the 10 year period, irrespective of the results of the first screen, or whether they received a BI as a result.

2.7 Incorporating Intervention costs from the Trial into SAPM

For each strategy in the trial, the long-term costs of implementation were estimated from the cost data collected in the trial, which is summarised in Table 3. Costs of training and printing literature were scaled up to national level using the estimates of the total numbers of practitioners and practices in each country. Costs of screening and delivering BIs were calculated from the number of screens, the number of positive screens and the number of BIs delivered estimated by the model using country- and strategy-specific estimates of the duration of BI delivery, multiplied by country-specific estimates of the per-minute staff costs. The duration of screening was assumed to be 30 seconds for the first question of the AUDIT-C tool and 130 seconds for the remaining 2 questions (assuming the patient does not reply that they do not drink to the first question) in line with previously published estimates (Purshouse et al. 2009).

Table 3 - Intervention cost data collected in the trial

Cost data	Source
Cost of printing literature for each strategy	Collected by WP5 country teams
Cost of delivering training for each strategy	Collected by WP5 country teams, using data on trainer and venue costs
Cost of practitioners receiving training for each strategy	Estimated from duration of training time, plus travel time and the staff costs of the recipients of the training
Cost of practitioners' time	Taken from published national estimates
Number of PHCUs	Taken from published national estimates
Number of practitioners	Taken from published national estimates

The costs of financial reimbursement were calculated using the country-specific incentive structures and the number of screens and BIs delivered estimated from the model. Where maximum payments per practice or practitioner were in place during the trial, these were included in all calculations, with 12-weekly payments being capped at these levels. All costs are presented in 2013 Euros. All costs and health benefits are discounted using locally-appropriate discount rates for each country. The discount rates and the cost-effectiveness/willingness-to-pay thresholds applied for each country are given in Appendix C. The time horizon for all models is 30 years in order to account for the time lags which exist between changes in alcohol consumption and changes in risk of alcohol-related harm (Holmes et al. 2012).

2.8 Health economic analysis

For all strategies and all analyses, overall net costs were calculated by combining the implementation costs (both of implementing the strategy and of delivering the SBIs) with the downstream savings in healthcare costs. In the first instance these net costs and the associated estimated gain in QALYs are compared to a counterfactual scenario in which no SBIs are delivered. This provides an estimate of the cost-effectiveness of delivering SBIs via each strategy against not delivering any SBIs. Whilst this is informative in terms of whether or not each scenario is better than nothing, Table 1 shows that nothing is not current practice. We therefore perform a further incremental analysis in which all strategies are ranked in order of the overall QALY gains, and the additional costs and additional QALY gains of each strategy are compared to the next most effective strategy. This gives an estimate of the incremental cost effectiveness of each strategy compared to

the next best option, which can then be compared with the appropriate national willingness-to-pay threshold (the maximum amount which the country is willing to pay for each additional QALY gained – see Table 7 for these thresholds and their sources). Strategies which are more expensive but produce smaller QALY gains than others are then excluded, as are those with incremental costs per QALY greater than the national threshold and those where the incremental cost per QALY is greater than a strategy which provides larger QALY gains. For a full description of the principles of incremental analysis, please see Section 2.3 & 2.4 of Gray et al. 2010.

The result of this process is the identification of a set of cost-effective strategies, with the strategy which provides the largest QALY gains within the acceptable national willingness-to-pay threshold being the optimal strategy for that country. An alternative method of considering these results is also presented – for each strategy we can calculate the net cost compared to current practice (i.e. control). We can then also estimate the monetary value of the QALYs gains which that strategy provides over and above control using the appropriate national willingness-to-pay threshold. By subtracting the net cost from this valuation of the net gain we can estimate the Net Monetary Benefit (NMB) of each strategy, with the strategy producing the greatest NMB representing the optimal strategy for each country.

3 RESULTS

3.1 Within-trial analysis

Compared to a counterfactual scenario in which no SBIs are delivered, all strategies (including control) are estimated to be cost-effective in all countries, with the exception of control, TS+eBI and TS+FR+eBI in Poland. Indeed, all strategies are estimated to be not just cost-effective, but even cost-saving (and health improving), compared to no SBI delivery, in Catalonia, England, the Netherlands and Sweden.

Table 4 - Within-trial analysis results for cost-effective strategies

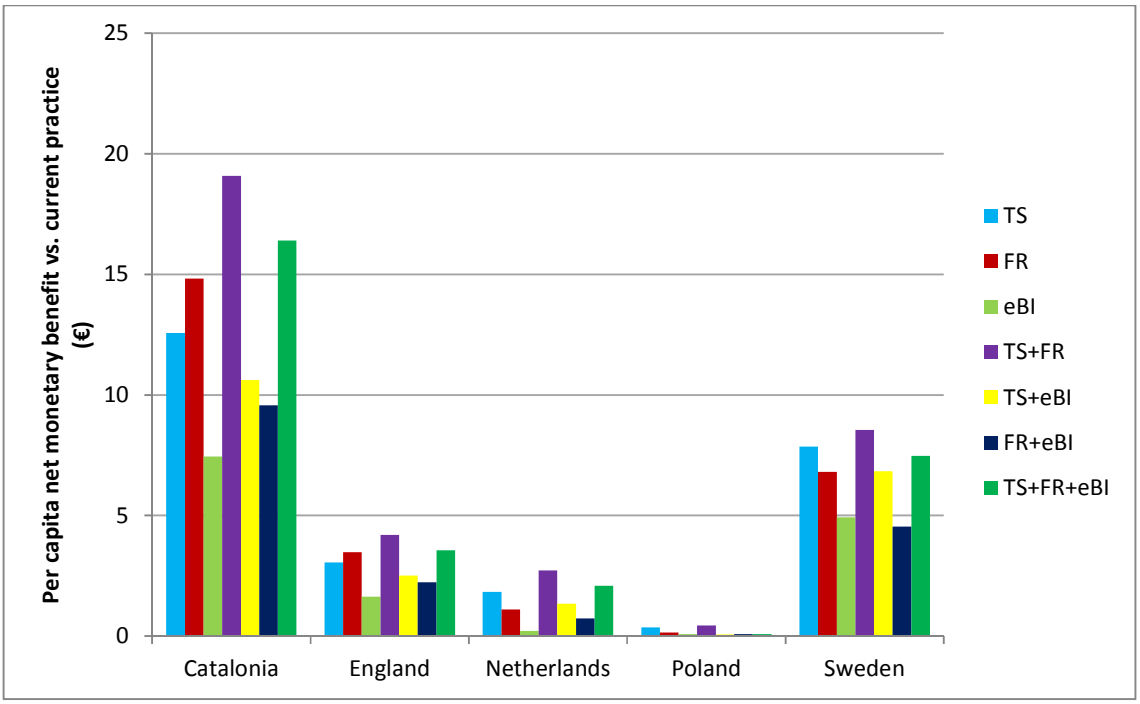
Country	Strategy	Net cost of programme (€m)	Net QALY gain vs. no SBIs (,000s)	Incremental cost (€m)	Incremental QALYs (,000s)	ICER (per QALY)
Catalonia	Control	-31.0	1.3			
	FR	-27.0	2.7	4.0	1.5	€ 2,721
	TS+FR	-25.2	3.2	1.8	0.4	€ 4,380
England	Control	-35.4	4.6			
	FR	-165.1	18.5	-129.6	13.8	Dominates
	TS+FR	-160.2	20.0	4.8	1.5	€ 3,250
Netherlands	Control	-4.0	1.0			
	FR	-11.2	2.3	-7.2	1.3	Dominates
	TS+FR	-6.7	3.4	4.5	1.1	€ 3,922
Poland	Control	0.8	0.1			
	TS+FR	3.7	2.7	2.9	2.7	€ 1,092
Sweden	Control	-51.1	3.9			
	TS+FR	-39.8	7.3	11.3	3.4	€ 3,279

The incremental analysis, comparing all 7 implemented strategies to the control arm in the trial produces a consistent finding that Training and Support combined with Financial Reimbursement (TS+FR) is the most effective strategy in terms of improving population health in the long-term. It is

also the most cost-effective strategy in all countries. The results and Incremental Cost-Effectiveness Ratios (ICERs) for all cost-effective strategies are shown in Table 4. Full results for all strategies are presented in Appendix D.

Figure 2 presents the Net Monetary Benefit analysis, confirming that TS+FR is the strategy which provides the greatest overall benefit in each country. This also illustrates that even though the ICERs for this strategy are similar across all 5 countries, the absolute gains in terms of benefit per capita are expected to be substantially larger in Catalonia and Sweden than the other countries, particularly Poland. For example, national implementation of TS+FR in Catalonia is estimated to produce a net gain of €19.08 per adult over 30 years, compared to €0.44 per adult in Poland.

Figure 2 - Net Monetary Benefit per capita for all strategies vs. current practice



3.2 Full implementation analysis

As for the within-trial analysis, results show that all strategies are cost-effective in all countries when compared to no SBI delivery, with the exception of Control and TS+eBI in Poland (see Table 6 and Table 10). An incremental analysis comparing all strategies to the control arm in the trial shows that Training and Support combined with Financial Reimbursement (TS+FR) is the most effective strategy in all countries. This is also the most cost-effective strategy in Catalonia, England, Poland and Sweden, whilst in the Netherlands the ICER compared to the next-best option (TS alone) is above the maximum threshold for cost-effectiveness, and therefore TS is the most cost-effective strategy in the Netherlands.

TS+FR is estimated to be cost-saving and health improving in England. TS+FR also has a low ICER of €4,632/QALY in Poland (vs. the next best option of TS alone). TS+FR also has a low ICER of €6,522/QALY (vs. control) in Sweden. In Catalonia the ICER versus the next most cost-effective option (TS alone) is considerably higher at €48,954/QALY, although this is still likely to be considered cost-effective. In the Netherlands where TS is the most cost-effective option, the TS strategy has an ICER of €3,386 compared to the next best option of eBI referral.

Detailed results for all cost-effective strategies are shown in Table 5, with detailed results for all strategies for England, the Netherlands and Poland presented in Table 6. Equivalent results for Catalonia and Sweden are given in Appendix E. Figure 3 illustrates the results for all strategies compared to control for all countries.

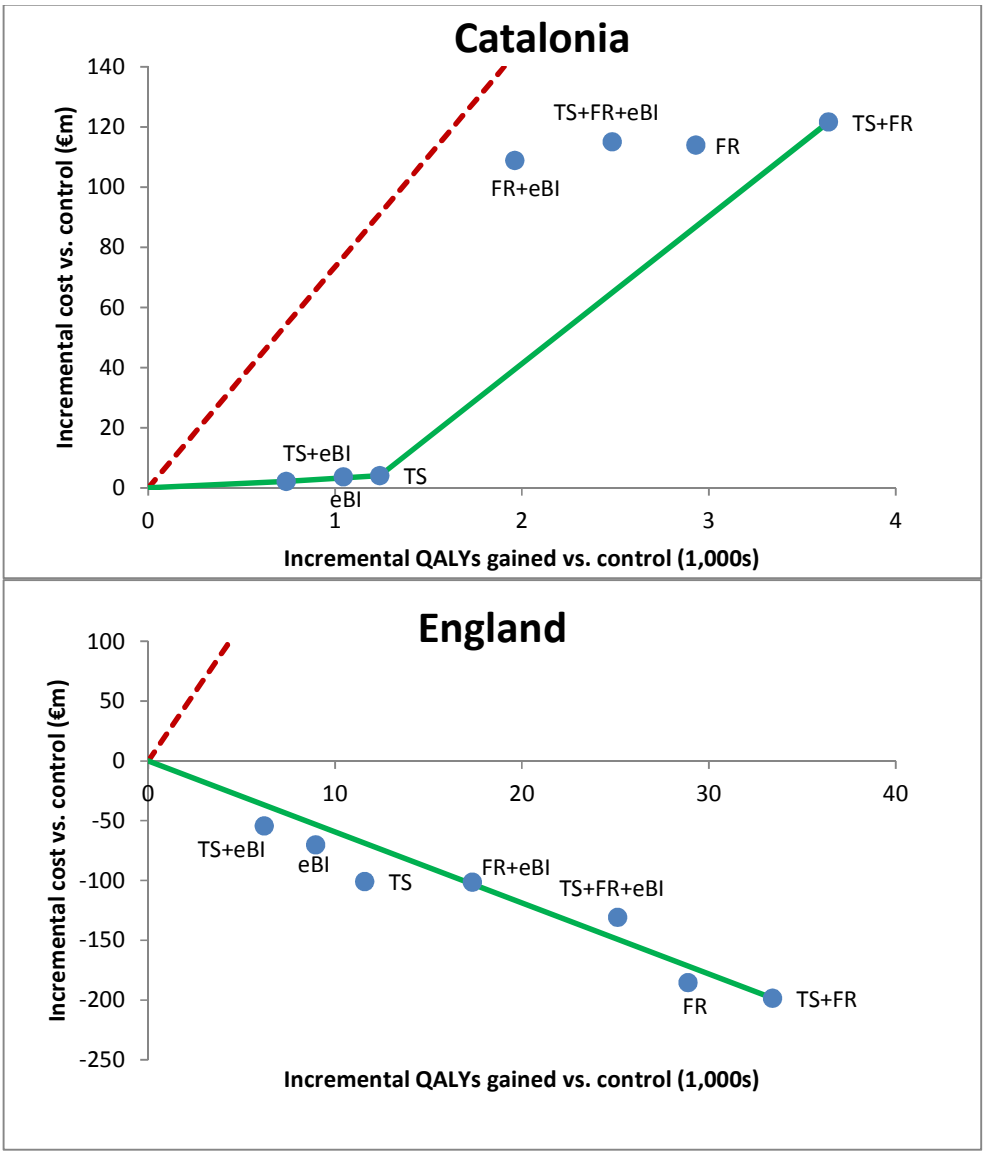
Table 5 – Full implementation analysis results for cost-effective strategies

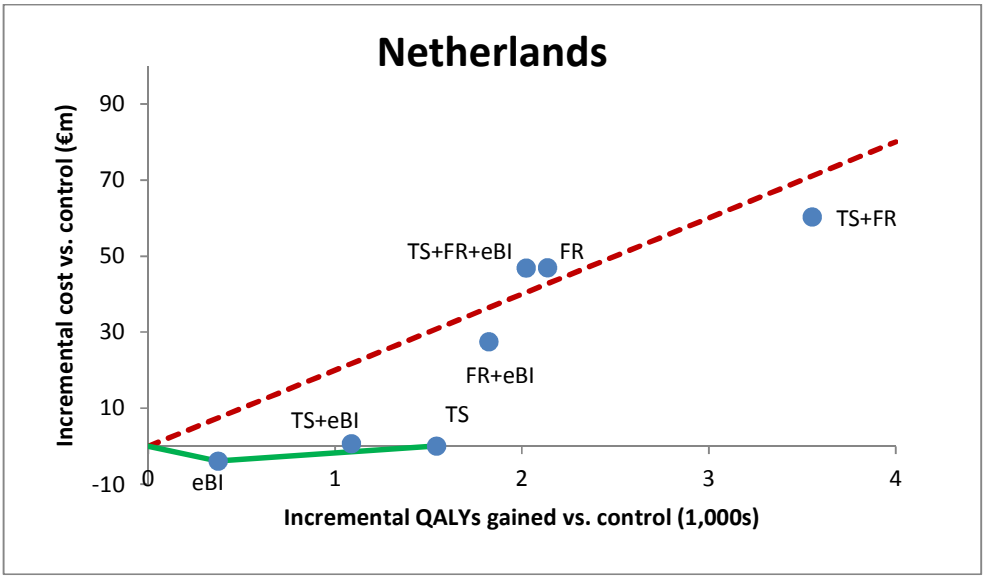
Country	Strategy	Net cost of programme (€m)	Net QALY gain vs. no SBIs (,000s)	Incremental cost (€m)	Incremental QALYs (,000s)	ICER (per QALY)
Catalonia	Control	-31.0	1.3			
	eBI	-28.9	2.0	2.1	0.7	€ 2,910
	TS	-27.0	2.5	1.9	0.5	€ 3,812
	TS+FR	90.5	4.9	117.5	2.4	€ 48,954
England	Control	-35.4	4.6			
	TS+FR	-233.8	38.0	-198.4	33.4	Dominates
Netherlands	Control	-4.0	1.0			
	eBI	-7.9	1.3	-3.9	0.4	Dominates
	TS	-3.9	2.5	4.0	1.2	€ 3,386
Poland	Control	0.8	0.1			
	TS	3.3	2.2	2.5	2.1	€ 1,168
	TS+FR	18.5	5.5	15.2	3.3	€ 4,632
Sweden	Control	-51.1	3.9			
	TS+FR	-10.7	10.1	40.3	6.2	€ 6,522

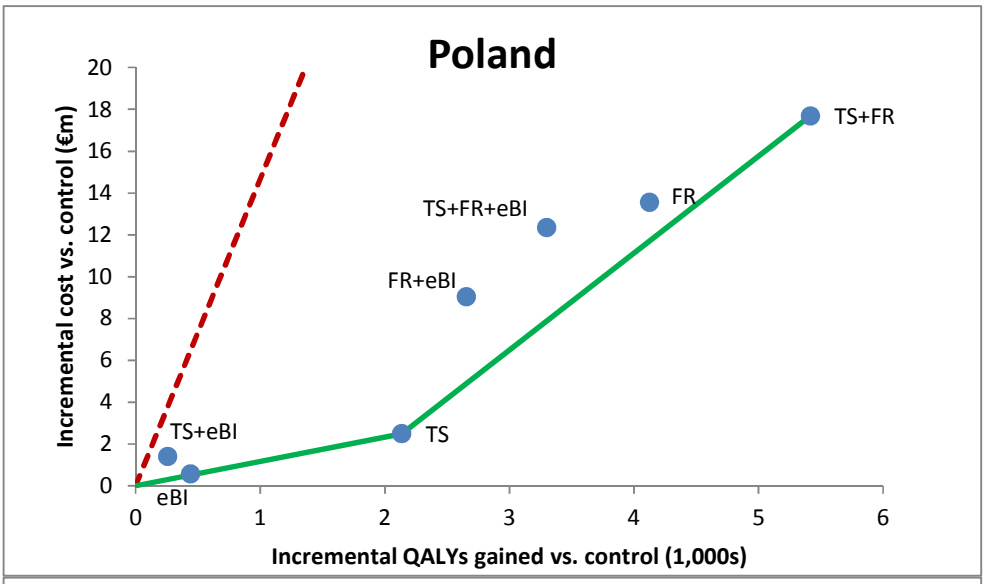
Figure 3 - Cost-effectiveness diagrams for all strategies in all countries.

N.B. Green lines represent the 'expansion path' – the set of cost-effective strategies ranked in increasing order of effectiveness.

Dashed red lines represent the cost-effectiveness threshold for each country – the maximum amount that the country is willing to pay for additional gains in health-related quality of life.




Netherlands
Incremental cost vs. control (€m)
90
70
50
30
10
-10
0
1
2
3
4
TS+FR
TS+FR+eBI
FR
FR+eBI
TS+eBI
TS
eBI
Incremental QALYs gained vs. control (1,000s)


Poland
Incremental cost vs. control (€m)
20
18
16
14
12
10
8
6
4
2
0
1
2
3
4
5
6
TS+FR
FR
TS+FR+eBI
FR+eBI
TS+eBI
TS
eBI
Incremental QALYs gained vs. control (1,000s)

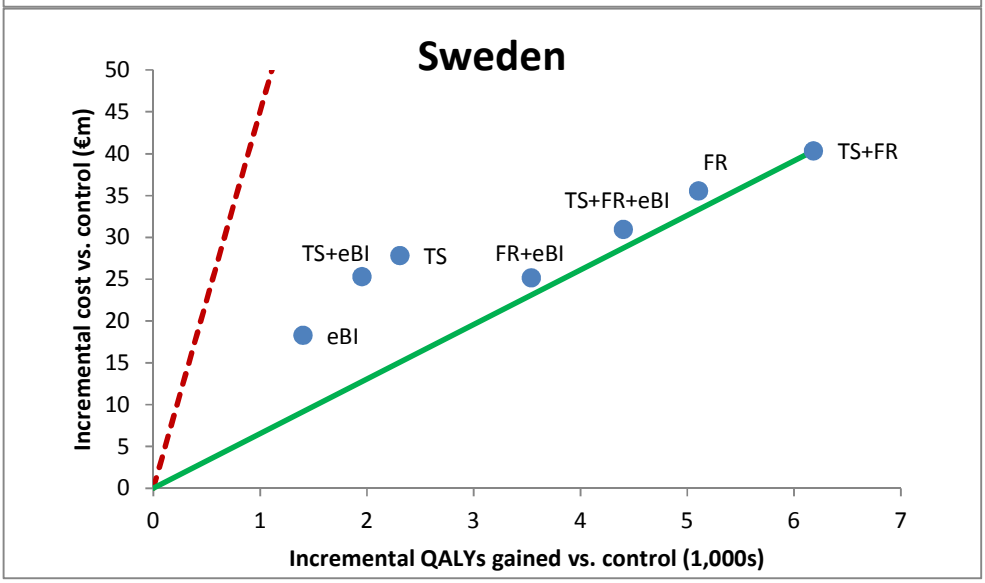
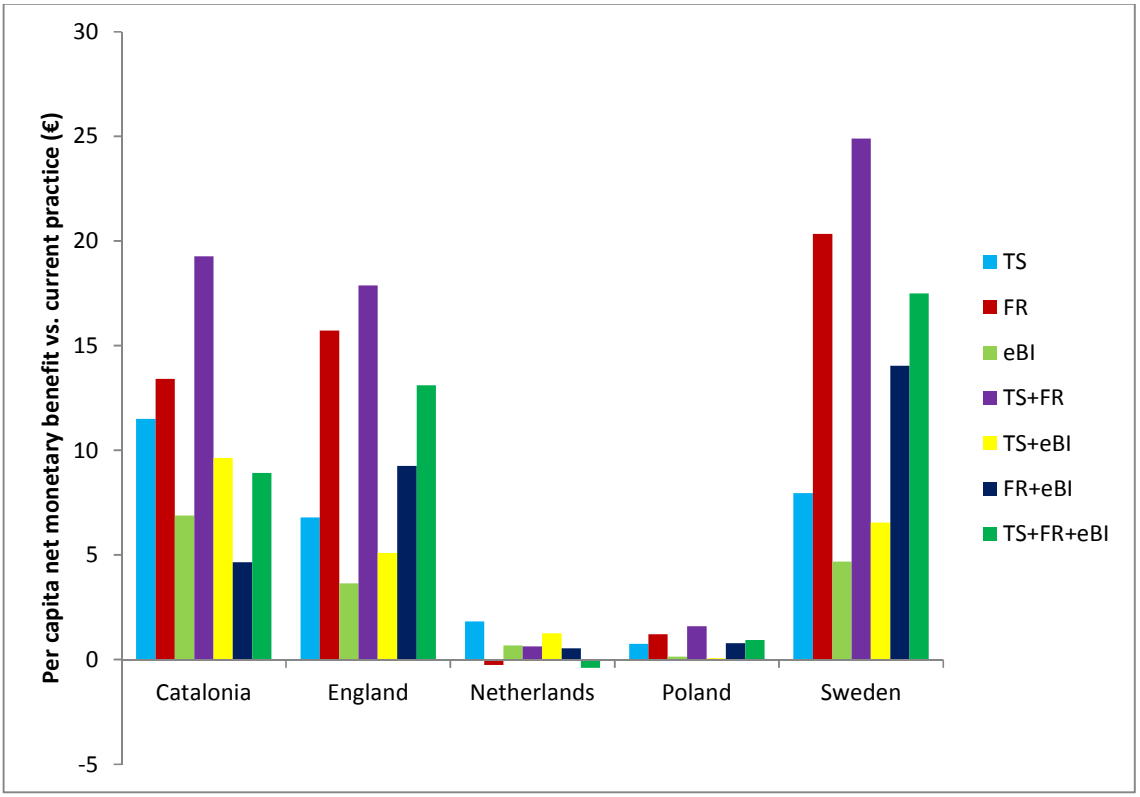

Sweden
Incremental cost vs. control (€m)
50
45
40
35
30
25
20
15
10
5
0
1
2
3
4
5
6
7
TS+FR
FR
TS+FR+eBI
TS+eBI
TS
FR+eBI
eBI
Incremental QALYs gained vs. control (1,000s)

Table 6 - Full implementation analysis: detailed results for England, Netherlands and Poland

		Versus no SBI delivery						Incremental versus control					
		Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	CER/QALY	Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	ICER
England	Control	14.34	0.00	49.79	-35.44	4.64	Dominates						
	TS	30.27	17.35	184.03	-136.40	16.23	Dominates	15.93	17.35	134.24	-100.96	11.59	Dominates
	FR	55.46	77.54	353.81	-220.81	33.53	Dominates	41.11	77.54	304.02	-185.37	28.89	Dominates
	eBI	22.13	8.68	120.42	-89.62	10.85	Dominates	7.78	8.68	70.63	-54.18	6.21	Dominates
	TS+FR	63.60	100.74	398.17	-233.83	38.05	Dominates	49.26	100.74	348.39	-198.39	33.41	Dominates
	TS+eBI	23.48	26.03	155.06	-105.55	13.60	Dominates	9.14	26.03	105.27	-70.11	8.96	Dominates
	FR+eBI	34.47	68.35	239.49	-136.67	21.99	Dominates	20.13	68.35	189.70	-101.23	17.35	Dominates
	TS+FR+eBI	40.22	101.90	308.47	-166.36	29.77	Dominates	25.87	101.90	258.69	-130.91	25.13	Dominates
Netherlands	Control	6.37	0.00	10.34	-3.96	0.97	Dominates						
	TS	14.74	8.59	27.24	-3.91	2.52	Dominates	8.37	8.59	16.90	0.05	1.54	€ 32
	FR	21.28	58.85	37.19	42.94	3.11	€ 13,814	14.91	58.85	26.85	46.91	2.14	€ 21,958
	eBI	9.96	0.02	17.85	-7.87	1.35	Dominates	3.59	0.02	7.52	-3.91	0.37	Dominates
	TS+FR	25.60	76.66	45.95	56.30	4.53	€ 12,439	19.22	76.66	35.62	60.26	3.55	€ 16,958
	TS+eBI	11.61	8.61	23.50	-3.28	2.06	Dominates	5.24	8.61	13.16	0.68	1.09	€ 629
	FR+eBI	14.06	36.69	27.25	23.49	2.80	€ 8,402	7.69	36.69	16.92	27.46	1.82	€ 15,055
	TS+FR+eBI	17.22	60.00	34.38	42.85	2.99	€ 14,309	10.85	60.00	24.04	46.81	2.02	€ 23,150
Poland	Control	0.78	0.05	0.01	0.83	0.06	€ 13,106						
	TS	2.87	0.66	0.21	3.32	2.20	€ 1,511	2.09	0.60	0.20	2.49	2.14	€ 1,168
	FR	4.79	10.04	0.44	14.38	4.19	€ 3,435	4.01	9.98	0.43	13.56	4.12	€ 3,287
	eBI	1.39	0.05	0.04	1.40	0.50	€ 2,793	0.61	0.00	0.03	0.58	0.44	€ 1,312
	TS+FR	5.75	13.33	0.56	18.52	5.48	€ 3,380	4.96	13.27	0.55	17.69	5.42	€ 3,266
	TS+eBI	1.61	0.66	0.03	2.23	0.32	€ 6,998	0.83	0.60	0.02	1.40	0.26	€ 5,490
	FR+eBI	2.50	7.64	0.26	9.87	2.72	€ 3,632	1.71	7.58	0.25	9.04	2.65	€ 3,407
	TS+FR+eBI	3.05	10.45	0.33	13.17	3.36	€ 3,918	2.27	10.40	0.32	12.35	3.30	€ 3,742

Across the 5 countries, whilst the details of the results differ, the broad patterns remain the same. TS+FR is amongst the most expensive strategies to implement (costing in excess of €100m over 10 years in Catalonia and England) but produces the greatest cost savings to healthcare services (e.g. €398m over 30 years in England) and the greatest corresponding health benefits (e.g. 5,480 QALYs over 30 years in Poland). This pattern is illustrated in Figure 4 which shows the per capita net benefit of each strategy over the 30 year time horizon of the model. For example, implementation of TS+FR is estimated to benefit Sweden by the equivalent of €24.90 for every adult over 30 years.

Figure 4 - Net Monetary Benefit per capita of all strategies vs. current practice



3.3 Sensitivity analyses

In order to investigate the uncertainty in our assumptions of continued effectiveness for strategies other than FR in the longer-term in the full implementation analysis, we tested the assumption that training had to be re-delivered every 5 or every 2 years in order to achieve this persistence of effect. The retraining was assumed to cost the same as the original training delivered in the trial (before discounting). Full results for these alternative assumptions can be found in Appendix F.

These alternative assumptions increased the implementation costs of all strategies, particularly those involving Training & Support. For example, the cost over 10 years of delivering TS in the Netherlands increased from €8.6m to €15.9m with retraining every 5 years and €36.9m with retraining every 2 years. However, these increased costs made little difference to the overall cost-effectiveness results and the overall conclusions of the analysis. The only significant change is that TS ceases to be cost-effective in the Netherlands if retraining is required every 2 years, with eBI referral becoming the most cost-effective option under this scenario.

4 DISCUSSION

4.1 Summary of results

The results of this analysis consistently show that Training and Support or Training and Support in combination with Financial Reimbursement are effective and cost-effective strategies for increasing the delivery rate of Screening and Brief Interventions in primary care. Modelling using only the trial data suggests that TS+FR is the most cost-effective strategy in all countries, whilst assuming that increased screening rates in practices receiving FR would be maintained if incentives continued to be paid (an assumption which is consistent with the findings of previous studies in the field, e.g. (Hamilton et al. 2014)) makes TS+FR the optimal strategy in 4 out of 5 countries. Sensitivity analyses show that these results are robust to assumptions about additional training costs being required in order to achieve long-term effectiveness.

There is substantial variation between countries in terms of the estimated scale and impact of the various strategies, as evidenced in Figure 2 and Figure 4. This variation is driven by a huge range of underlying differences between the 5 countries, in terms of alcohol consumption (both mean levels of consumption and patterns of drinking), frequency of primary care consultations (which is over twice as high on average in the Netherlands as in Sweden (OECD 2012), for example), rates of alcohol-related harm and the healthcare costs of treatment and practitioners' time as well as substantial differences in SBI delivery measures at baseline (as illustrated in Table 1). For example, Catalonia has a markedly lower screen positive rate than the other 4 countries, while Poland has the lowest screening rate, but the highest conversion rate from positive screens to Brief Interventions delivered. These differences interact with the different impact of the 8 strategies on each of the 3 outcomes measures, leading to different changes in population alcohol consumption and consequent changes in alcohol-related hospitalisation and mortality rates and associated healthcare costs. In spite of this heterogeneity, the analysis shows a clear picture across all 5 countries, suggesting that the conclusions are likely to be applicable to other countries with their own unique drinking and primary care contexts.

4.2 Limitations

There are a number of limitations to this analysis, primarily related to the complexity of the trial and the necessary complexity of the analysis in order to adequately capture the full heterogeneity both between countries at baseline as discussed above, and in the impacts of the trialled strategies on screening, screen positive and BI delivery rates. A key limitation is the fact that results for Catalonia and Sweden have been evaluated using a different, generalised, model, to those for England, the Netherlands and Poland, which were analysed using dedicated country-specific models. However, results across both model types are consistent, and exclusion of the Catalan and Swedish results would not change the overall conclusions of the analysis. Additionally, there are a number of limitations inherent in both modelling methodologies, which were discussed in detail in the previous deliverable D3.1.

There are also a number of additional assumptions relating to the interpretation of the trial data which should be considered when interpreting the results of this analysis. One key area of uncertainty concerns the assumptions of ongoing effect of the 8 strategies following the 6-month follow-up in the trial. We have examined some of these assumptions in sensitivity analyses reported above, and it should also be noted that, as most people visit their family doctor relatively frequently

(mean consultation frequency is 6.3 times per year across the EU (OECD 2012)), any strategy which increases screening rates will have a substantially larger impact in the first year following implementation than in subsequent years, when a large proportion of eligible patients will already have visited their doctor and been screened. The impact of alternative assumptions of effect in the longer-term are therefore likely to be small compared to the impact in the first year of implementation.

One final assumption of note is the fact that the trial did not collect data on the demographics (or alcohol consumption) of those patients who consulted with, but were not screened by participating practitioners. It is therefore difficult to determine whether increases in the rates of patients screening positive were a consequence of practitioners screening patients from different age-gender groups which have a higher prevalence of risky drinking behaviour, or due to practitioners screening the same number of patients in each age-gender group but with more successful identification of risky drinkers within each group. We have assumed the latter, but the impact of this assumption on the model results is unclear as it will depend on the distribution of alcohol consumption and alcohol-related harms across the population in each country. We hope to explore this assumption further in the future through analysis of Catalan online records from the trial which can give the demographics of the patients who were seen by their doctor but not screened during the trial.

5 CONCLUSIONS AND RECOMMENDATIONS FOR POLICY/FUTURE RESEARCH

5.1 Key findings

A. Large-scale, national-level programmes of Screening and Brief Interventions in primary care (e.g. screening all patients at their next GP consultation) are highly likely to be cost-effective in Italy, the Netherlands, Poland and England if fully implemented

B. Policy makers should be mindful of the short-term budgetary implications of such programmes

C. In general SBI programmes are estimated to be more expensive in countries with higher alcohol-related mortality, where more people will be captured by the programme and with lower alcohol-related morbidity rates. The health impact of an SBI policy is estimated to be greater in countries where alcohol consumption is greater and where more people are screened

D. Training and Support, combined with Financial Reimbursement, is the most effective measure to increase the delivery of SBIs amongst primary care practitioners. It is estimated to be cost-effective or cost-saving in Catalonia, England, Poland and Sweden, while Training and Support alone is estimated to be the most cost-effective strategy in the Netherlands.

5.2 Conclusions

A. The results presented previously in Deliverable D3.1 show that SBI programmes with full participation from practitioners are highly likely to be a cost-effective measure for tackling alcohol-related harm across Europe.

B. In practice, participation is only partial, for example, SBIs are already recommended for use in primary care in Sweden, the Netherlands and England, yet the screening rates recorded at baseline in the WP5 trial were only 4.6-10.6%, and it is likely that this is an overestimate of the true rate, since participating providers may well have been affected by an intervention or 'Hawthorne' effect, increasing their SBI delivery behaviour, even before the trial implementation began.

C. The analysis presented in this addendum shows that Training and Support combined with Financial Reimbursement (TS+FR) provides an effective and potentially cost-effective method to increase these rates and to begin to work towards the target of full uptake.

D. However, this field of implementation science is complex and heterogeneous and it is unlikely that any single approach will resolve all obstacles preventing high levels of SBI delivery in primary care (Colom et al. 2014).

5.3 Recommendations for future research

Deliverable D3.1 highlighted a number of areas for further research, including

- Research would be useful on the impact of SBIs on patterns of drinking and heterogeneity in response to SBIs amongst different population groups (by age, gender, drinking levels, socioeconomic or other factors)

- Research would be useful to gain a greater understanding of underreporting of alcohol consumption and how this varies across and within populations.

This addendum further recommends research into

- What are the effective components of Training and Support programmes?

- What would be the optimal incentive structure to improve SBI delivery?

- How do practitioners change their screening behaviour in response to different interventions?

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7 APPENDICES

7.1 Appendix A: Estimating 'arrival profiles' for each scenario

In order to estimate the impact of any SBI policy it is important to understand how the coverage of the policy will vary across the population. As part of the development of the country-specific models for England, the Netherlands and Poland, data was collected on the proportion of each age-gender group of the population who would be screened in each year of a policy of screening everybody at their next consultation with a family doctor. We refer to this data as the 'arrival profile' of the policy. In effect this equates to a screening rate (as defined in the trial) of 100%.

The challenge that must be overcome to model lower screening rates (such as those observed in the ODHIN trial and shown in Table 1) is that people in different age and gender groups not only have different rates of visiting their family doctor at least once, but also different numbers of visits within the year. Thus if the screening rate is 50% (i.e. half of all eligible patients walking through the door of their family doctor will be screened), older patients and women who tend to consult more frequently will have more opportunities to be screened and thus have a higher cumulative probability of screening across the year.

In order to address this issue we purchased data from the Netherlands Information Network of General Practice (LINH) which gave the proportion of each age-gender group visiting their family doctor at least once in a year, and the average number of consultations in that year for those with at least one consultation. This data covers 5 years and also includes information on patients consulting in year 2 who had not consulted at all during year 1, those who consulted in year 3 who had not consulted in years 1 or 2 and so on.

The richness of this data allowed us to estimate the proportion of each age-gender subgroup of the Dutch population who would be screened in each year over 5 years for any given screening rate. As the trial is focused on a 6-month window, we further decomposed the consultation frequencies for the first year into monthly probabilities, under the assumption that consultations are distributed uniformly across the year.

We then constructed a model which takes as an input the overall screening rate for each month in the first year and then for each subsequent year from 2-5 after that, as estimated from the trial data. This model uses the LINH data to estimate the proportion of the Dutch population who would be screened over 5 years for these changing screening rates. Gamma distributions were then fitted to the 5 year figures to produce estimates of the proportion of the population screened in years 6-10.

For the other 4 countries, we had existing arrival profiles for a screening rate of 100% estimated as part of the development of the country-specific models. These existing profiles were then adjusted by multiplying the country-specific 100% profile by the ratio between Dutch 100% profile and the outputs of the model described above for the strategy being modelled.

7.2 Appendix B: Screening model parameters

For all of the country-specific models, the probability of any individual screening positively on any given screening tool is estimated from a logistic regression of the form:

Equation 4:

$$P(Screen\ positive) = \frac{e^{(\beta_1 * Mean\ consumption + \beta_2 + constant)}}{1 + e^{(\beta_1 * Mean\ consumption + \beta_2 + constant)}}$$

where β_2 is an age-gender group-specific coefficient. The coefficients in the regression are estimated from the 2000 and 2007 UK Adult Psychiatric Morbidity Surveys, which include data on respondents' age, gender, alcohol consumption and scores on a range of common alcohol screening tools such as AUDIT, AUDIT-C and FAST. For the analysis conducted here, regressions were fitted to estimate the probability of screening positive on AUDIT-C with thresholds of 4 and 5. Within the country models, every individual who is screened is randomly allocated to screening positive or negative based on their probability of screening positive predicted from this regression.

This process means that every country model has an implied screen positive rate, since this is the proportion of individuals screened under any strategy who screen positive. These rates may not necessarily match those screen positive rates observed for the same strategy in the trial. In order to address this discrepancy, and to better account for the impact of each strategy on screen positive rates, a single additional coefficient, α, is estimated for each strategy in each country such that the following equation is satisfied:

Equation 5:

$$Screen\ positive\ rate\ from\ trial = \frac{\sum_i weight_i * \left(\frac{e^{(\alpha * \beta_1 * Mean\ consumption_i + \alpha * \beta_{2i} + \alpha * constant)}}{1 + e^{(\alpha * \beta_1 * Mean\ consumption_i + \alpha * \beta_{2i} + \alpha * constant)}}\right)}{\sum_i weight_i}$$

where *i* represents the individuals who populate the country-specific model and $weight_i$ their corresponding weighting within the model. The adjusted version of Equation 4, incorporating the value of α is then used within the model when predicting the probability of any individual screening positive. This calibration ensures that the implied screen rates from the model match those observed within the trial.

7.3 Appendix C: Cost-effectiveness thresholds and discount rates by country

Table 7 - Cost-effectiveness thresholds by country

Country	Cost-effectiveness threshold per QALY	Source
Catalonia	€ 73,500	No specific threshold, so 3xGDP used as recommended by Hutubessy et al. 2003
England	£20,000	(National Institute of Health and Clinical Excellence (NICE) 2013)
Netherlands	€ 20,000	(Niessen et al. 2007)
Poland	26,750 zł	Mid point of 12500-41000zł range from Orlewska & Mierzejewski 2004
Sweden	€ 45,000	(Persson et al. n.d.)

Table 8 - Discount rates by country

Country	Discount rate for costs	Discount rate for health outcomes	Source
Catalonia	3.0%	3.0%	(International Society for Pharmacoeconomics and Outcomes Research 2011)
England	3.5%	3.5%	(National Institute of Health and Clinical Excellence (NICE) 2013)
Netherlands	4.0%	1.5%	(College Voor Zorkverzekeringen 2010)
Poland	5.0%	5.0%	(Orlewska & Mierzejewski 2004)
Sweden	3.0%	3.0%	(International Society for Pharmacoeconomics and Outcomes Research 2013)

7.4 Appendix D: Full within-trial analysis results for all countries

Table 9 - Within-trial analysis: full results for all countries

		Versus no SBIs						Incremental versus control					
		Screening Cost (€m)[2]	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	CER/QALY	Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	ICER/QALY
Catalonia	Control	-31.05	0.00	0	-31.05	1.3	Dominates						
	TS	-27.68	0.69	0	-26.99	2.5	Dominates	3.37	0.69	0.00	4.06	1.24	€ 3,275
	FR in trial	-27.05	0.00	0	-27.04	2.7	Dominates	4.00	0.00	0.00	4.01	1.47	€ 2,721
	eBI	-29.04	0.14	0	-28.90	2.0	Dominates	2.01	0.14	0.00	2.15	0.74	€ 2,910
	TS+FR in trial	-25.92	0.69	0	-25.23	3.2	Dominates	5.13	0.69	0.00	5.82	1.89	€ 3,086
	TS+eBI	-28.21	0.83	0	-27.38	2.3	Dominates	2.84	0.83	0.00	3.67	1.04	€ 3,513
	FR+eBI in trial	-28.47	0.14	0	-28.32	2.2	Dominates	2.58	0.14	0.00	2.73	0.95	€ 2,871
	TS+FR+eBI in trial	-26.65	0.83	0	-25.81	2.9	Dominates	4.40	0.83	0.00	5.23	1.62	€ 3,233
England	Control	14.34	0.00	49.79	-35.44	4.64	Dominates						
	TS	30.27	17.35	184.03	-136.40	16.23	Dominates	15.93	17.35	134.24	-100.96	11.59	Dominates
	FR in trial	32.88	0.12	198.05	-165.06	18.47	Dominates	18.53	0.12	148.27	-129.62	13.83	Dominates
	eBI	22.13	8.68	120.42	-89.62	10.85	Dominates	7.78	8.68	70.63	-54.18	6.21	Dominates
	TS+FR in trial	36.97	17.47	214.67	-160.22	19.95	Dominates	22.63	17.47	164.88	-124.78	15.31	Dominates
	TS+eBI	23.48	26.03	155.06	-105.55	13.60	Dominates	9.14	26.03	105.27	-70.11	8.96	Dominates
	FR+eBI in trial	23.71	8.80	161.19	-128.68	13.97	Dominates	9.37	8.79	111.40	-93.24	9.33	Dominates
	TS+FR+eBI in trial	27.19	26.15	175.68	-122.35	16.80	Dominates	12.84	26.14	125.89	-86.91	12.16	Dominates
Netherlands	Control	6.37	0.00	10.34	-3.96	0.97	Dominates						
	TS	14.74	8.59	27.24	-3.91	2.52	Dominates	8.37	8.59	16.90	0.05	1.54	€ 32
	FR in trial	15.78	0.00	26.96	-11.17	2.26	Dominates	9.41	0.00	16.62	-7.21	1.28	Dominates
	eBI	9.96	0.02	17.85	-7.87	1.35	Dominates	3.59	0.02	7.52	-3.91	0.37	Dominates
	TS+FR in trial	18.57	8.59	33.87	-6.71	3.39	Dominates	12.20	8.59	23.53	-2.75	2.42	Dominates
	TS+eBI	11.61	8.61	23.50	-3.28	2.06	Dominates	5.24	8.61	13.16	0.68	1.09	€ 629
	FR+eBI in trial	11.42	0.02	22.05	-10.61	1.91	Dominates	5.05	0.02	11.72	-6.65	0.94	Dominates
	TS+FR+eBI in trial	14.20	8.61	30.33	-7.52	2.91	Dominates	7.82	8.61	19.99	-3.56	1.93	Dominates

[2] For the countries where results are estimated using a meta-model it is not possible to separate out the costs of screening from the downstream hospital cost savings and the negative figures in this column for Catalonia and Sweden therefore represent the overall net cost to the Health Service.

		Versus no SBIs						Incremental versus baseline					
		Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	ICER	Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	ICER
Poland	Control	0.78	0.05	0.01	0.83	0.06	€ 13,106						
	TS	2.87	0.66	0.21	3.32	2.20	€ 1,511	2.09	0.60	0.20	2.49	2.14	€ 1,168
	FR in trial	2.35	0.06	0.07	2.34	0.89	€ 2,642	1.57	0.00	0.06	1.51	0.82	€ 1,840
	eBI	1.39	0.05	0.04	1.40	0.50	€ 2,793	0.61	0.00	0.03	0.58	0.44	€ 1,312
	TS+FR in trial	3.33	0.66	0.27	3.72	2.71	€ 1,371	2.55	0.60	0.26	2.89	2.65	€ 1,092
	TS+eBI	1.61	0.66	0.03	2.23	0.32	€ 6,998	0.83	0.60	0.02	1.40	0.26	€ 5,490
	FR+eBI in trial	1.62	0.06	0.04	1.64	0.51	€ 3,198	0.84	0.00	0.03	0.81	0.45	€ 1,803
	TS+FR+eBI in trial	1.77	0.66	0.04	2.39	0.35	€ 6,776	0.99	0.60	0.03	1.56	0.29	€ 5,397
Sweden	Control	-51.39	0.34	0.00	-51.06	3.88	Dominates						
	TS	-45.11	21.87	0.00	-23.24	6.19	Dominates	6.28	21.54	0.00	27.82	2.31	€ 12,042
	FR in trial	-43.97	2.04	0.00	-41.93	6.61	Dominates	7.42	1.70	0.00	9.13	2.73	€ 3,343
	eBI	-47.58	14.82	0.00	-32.76	5.28	Dominates	3.81	14.49	0.00	18.30	1.40	€ 13,057
	TS+FR in trial	-42.05	2.26	0.00	-39.79	7.32	Dominates	9.34	1.93	0.00	11.27	3.44	€ 3,279
	TS+eBI	-46.07	20.32	0.00	-25.75	5.84	Dominates	5.32	19.99	0.00	25.31	1.96	€ 12,938
	FR+eBI in trial	-46.52	2.18	0.00	-44.34	5.67	Dominates	4.88	1.84	0.00	6.72	1.79	€ 3,748
	TS+FR+eBI in trial	-43.32	2.80	0.00	-40.52	6.85	Dominates	8.07	2.47	0.00	10.54	2.97	€ 3,551

7.5 Appendix E: Full implementation analysis results for Catalonia and Sweden

Table 10 - Full implementation analysis: full results for Catalonia and Sweden

		Versus no SBIs						Incremental versus baseline					
		Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)[3]	Net cost (€m)	QALYs gained (,000s)	ICER	Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	ICER
Catalonia	Control	-31.05	0.00	0	-31.05	1.3	Dominates						
	TS	-27.68	0.69	0	-26.99	2.5	Dominates	3.37	0.69	0.00	4.06	1.24	€ 3,275
	FR in trial	-23.08	105.92	0	82.84	4.2	€ 19,698	7.97	105.92	0.00	113.89	2.93	€ 38,865
	eBI	-29.04	0.14	0	-28.90	2.0	Dominates	2.01	0.14	0.00	2.15	0.74	€ 2,910
	TS+FR in trial	-21.15	111.69	0	90.54	4.9	€ 18,420	9.90	111.69	0.00	121.59	3.64	€ 33,403
	TS+eBI	-28.21	0.83	0	-27.38	2.3	Dominates	2.84	0.83	0.00	3.67	1.04	€ 3,513
	FR+eBI in trial	-25.72	103.50	0	77.78	3.2	€ 24,034	5.33	103.50	0.00	108.83	1.96	€ 55,493
	TS+FR+eBI in trial	-24.30	108.30	0	84.00	3.8	€ 22,349	6.75	108.30	0.00	115.05	2.48	€ 46,327
Sweden	Control	-51.39	0.34	0.00	-51.06	3.88	Dominates						
	TS	-45.11	21.87	0.00	-23.24	6.19	Dominates	6.28	21.54	0.00	27.82	2.31	€ 12,042
	FR in trial	-37.50	22.00	0.00	-15.50	8.99	Dominates	13.89	21.67	0.00	35.56	5.11	€ 6,961
	eBI	-47.58	14.82	0.00	-32.76	5.28	Dominates	3.81	14.49	0.00	18.30	1.40	€ 13,057
	TS+FR in trial	-34.58	23.85	0.00	-10.73	10.06	Dominates	16.81	23.51	0.00	40.33	6.18	€ 6,522
	TS+eBI	-46.07	20.32	0.00	-25.75	5.84	Dominates	5.32	19.99	0.00	25.31	1.96	€ 12,938
	FR+eBI in trial	-41.77	15.87	0.00	-25.89	7.42	Dominates	9.63	15.54	0.00	25.16	3.54	€ 7,108
	TS+FR+eBI in trial	-39.42	19.31	0.00	-20.11	8.28	Dominates	11.97	18.98	0.00	30.95	4.40	€ 7,031

[3] See footnote to Table 8

7.6 Appendix F: Full sensitivity results for all countries

Table 11 – Full sensitivity analysis results for Catalonia

			Versus no SBIs						Incremental versus baseline					
			Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	CER/QALY	Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	ICER/QALY
Catalonia	Retraining every 5 years	Control	-31.05	0.00	0.00	-31.05	1.28	Dominates						
		TS	-27.68	1.30	0.00	-26.38	2.51	Dominates	3.37	1.30	0.00	4.67	1.24	€ 3,768
		FR	-23.08	105.92	0.00	82.84	4.21	€ 19,698	7.97	105.92	0.00	113.89	2.93	€ 38,865
		eBI	-29.04	0.27	0.00	-28.78	2.01	Dominates	2.01	0.27	0.00	2.27	0.74	€ 3,080
		TS+FR	-21.15	112.30	0.00	91.15	4.92	€ 18,545	9.90	112.30	0.00	122.20	3.64	€ 33,571
		TS+eBI	-28.21	1.57	0.00	-26.65	2.32	Dominates	2.84	1.57	0.00	4.40	1.04	€ 4,219
		FR+eBI	-25.72	103.62	0.00	77.91	3.24	€ 24,073	5.33	103.62	0.00	108.96	1.96	€ 55,557
		TS+FR+eBI	-24.30	109.03	0.00	84.74	3.76	€ 22,545	6.75	109.03	0.00	115.79	2.48	€ 46,623
	Retraining every 2 years	Control	-31.05	0.00	0.00	-31.05	1.28	Dominates						
		TS	-27.68	3.07	0.00	-24.61	2.51	Dominates	3.37	3.07	0.00	6.44	1.24	€ 5,195
		FR	-23.08	105.92	0.00	82.84	4.21	€ 19,699	7.97	105.92	0.00	113.89	2.93	€ 38,866
		eBI	-29.04	0.63	0.00	-28.41	2.01	Dominates	2.01	0.63	0.00	2.64	0.74	€ 3,570
		TS+FR	-21.15	114.07	0.00	92.92	4.92	€ 18,905	9.90	114.07	0.00	123.97	3.64	€ 34,057
		TS+eBI	-28.21	3.70	0.00	-24.52	2.32	Dominates	2.84	3.70	0.00	6.53	1.04	€ 6,260
		FR+eBI	-25.72	103.99	0.00	78.27	3.24	€ 24,185	5.33	103.99	0.00	109.32	1.96	€ 55,742
		TS+FR+eBI	-24.30	111.16	0.00	86.87	3.76	€ 23,112	6.75	111.16	0.00	117.92	2.48	€ 47,481

Table 12 - Full sensitivity analysis results for England

			Versus no SBIs						Incremental versus baseline					
			Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	CER/QALY	Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	ICER/QALY
England	Retraining every 5 years	Control	14.34	0.01	49.79	-35.44	4.64	Dominates						
		TS	30.27	32.48	184.03	-121.28	16.23	Dominates	15.93	32.47	134.24	-85.84	11.59	Dominates
		FR	55.46	77.65	353.81	-220.71	33.53	Dominates	41.11	77.64	304.02	-185.27	28.89	Dominates
		eBI	22.13	16.24	120.42	-82.05	10.85	Dominates	7.78	16.23	70.63	-46.62	6.21	Dominates
		TS+FR	63.60	115.96	398.17	-218.61	38.05	Dominates	49.26	115.96	348.39	-183.17	33.41	Dominates
		TS+eBI	23.48	48.71	155.06	-82.86	13.60	Dominates	9.14	48.70	105.27	-47.43	8.96	Dominates
		FR+eBI	34.47	76.01	239.49	-129.01	21.99	Dominates	20.13	76.00	189.70	-93.57	17.35	Dominates
		TS+FR+eBI	40.22	124.69	308.47	-143.57	29.77	Dominates	25.87	124.68	258.69	-108.14	25.13	Dominates
	Retraining every 2 years	Control	14.34	0.02	49.79	-35.43	4.64	Dominates						
		TS	30.27	75.97	184.03	-77.78	16.23	Dominates	15.93	75.96	134.24	-42.35	11.59	Dominates
		FR	55.46	77.94	353.81	-220.42	33.53	Dominates	41.11	77.92	304.02	-184.99	28.89	Dominates
		eBI	22.13	37.99	120.42	-60.30	10.85	Dominates	7.78	37.98	70.63	-24.87	6.21	Dominates
		TS+FR	63.60	159.75	398.17	-174.83	38.05	Dominates	49.26	159.73	348.39	-139.40	33.41	Dominates
		TS+eBI	23.48	113.95	155.06	-17.63	13.60	Dominates	9.14	113.94	105.27	17.80	8.96	€ 1,988
		FR+eBI	34.47	98.05	239.49	-106.97	21.99	Dominates	20.13	98.03	189.70	-71.54	17.35	Dominates
		TS+FR+eBI	40.22	190.21	308.47	-78.05	29.77	Dominates	25.87	190.19	258.69	-42.62	25.13	Dominates

Table 13 - Full sensitivity analysis results for the Netherlands

			Versus no SBIs						Incremental versus baseline					
			Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	CER/QALY	Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	ICER/QALY
The Netherlands	Retraining every 5 years	Control	6.37	0.00	10.34	-3.96	0.97	Dominates						
		TS	14.74	15.93	27.24	3.43	2.52	€ 1,362	8.37	15.93	16.90	7.39	1.54	€ 4,788
		FR	21.28	58.85	37.19	42.94	3.11	€ 13,814	14.91	58.85	26.85	46.91	2.14	€ 21,958
		eBI	9.96	0.04	17.85	-7.86	1.35	Dominates	3.59	0.04	7.52	-3.89	0.37	Dominates
		TS+FR	25.60	84.00	45.95	63.64	4.53	€ 14,061	19.22	84.00	35.62	67.60	3.55	€ 19,023
		TS+eBI	11.61	15.96	23.50	4.08	2.06	€ 1,979	5.24	15.96	13.16	8.04	1.09	€ 7,397
		FR+eBI	14.06	36.70	27.25	23.51	2.80	€ 8,408	7.69	36.70	16.92	27.47	1.82	€ 15,064
		TS+FR+eBI	17.22	67.36	34.38	50.20	2.99	€ 16,765	10.85	67.36	24.04	54.17	2.02	€ 26,788
	Retraining every 2 years	Control	6.37	0.00	10.34	-3.96	0.97	Dominates						
		TS	14.74	36.93	27.24	24.43	2.52	€ 9,709	8.37	36.93	16.90	28.39	1.54	€ 18,395
		FR	21.28	58.85	37.19	42.94	3.11	€ 13,814	14.91	58.85	26.85	46.91	2.14	€ 21,958
		eBI	9.96	0.08	17.85	-7.81	1.35	Dominates	3.59	0.08	7.52	-3.85	0.37	Dominates
		TS+FR	25.60	105.00	45.95	84.64	4.53	€ 18,700	19.22	105.00	35.62	88.60	3.55	€ 24,933
		TS+eBI	11.61	37.01	23.50	25.12	2.06	€ 12,200	5.24	37.01	13.16	29.09	1.09	€ 26,759
		FR+eBI	14.06	36.75	27.25	23.56	2.80	€ 8,425	7.69	36.75	16.92	27.52	1.82	€ 15,090
		TS+FR+eBI	17.22	88.41	34.38	71.25	2.99	€ 23,794	10.85	88.41	24.04	75.22	2.02	€ 37,197

Table 14 - Full sensitivity analysis results for Poland

			Versus no SBIs						Incremental versus baseline					
			Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	CER/QALY	Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	ICER/QALY
Poland	Retraining every 5 years	Control	0.78	0.10	0.01	0.87	0.06	€ 13,815						
		TS	2.87	1.20	0.21	3.86	2.20	€ 1,756	2.09	1.10	0.20	2.99	2.14	€ 1,400
		FR	4.79	6.18	0.44	10.53	4.19	€ 2,514	4.01	6.08	0.43	9.65	4.12	€ 2,341
		eBI	1.39	0.10	0.04	1.45	0.50	€ 2,882	0.61	0.00	0.03	0.58	0.44	€ 1,312
		TS+FR	5.75	13.50	0.56	18.70	5.48	€ 3,412	4.96	13.40	0.55	17.82	5.42	€ 3,291
		TS+eBI	1.61	1.20	0.03	2.77	0.32	€ 8,689	0.83	1.10	0.02	1.90	0.26	€ 7,423
		FR+eBI	2.50	3.41	0.26	5.65	2.72	€ 2,077	1.71	3.31	0.25	4.77	2.65	€ 1,798
		TS+FR+eBI	3.05	6.10	0.33	8.82	3.36	€ 2,622	2.27	6.00	0.32	7.95	3.30	€ 2,408
	Retraining every 2 years	Control	0.78	0.23	0.01	1.00	0.06	€ 15,825						
		TS	2.87	2.72	0.21	5.39	2.20	€ 2,451	2.09	2.50	0.20	4.39	2.14	€ 2,056
		FR	4.79	6.31	0.44	10.65	4.19	€ 2,544	4.01	6.08	0.43	9.65	4.12	€ 2,341
		eBI	1.39	0.23	0.04	1.58	0.50	€ 3,135	0.61	0.00	0.03	0.58	0.44	€ 1,312
		TS+FR	5.75	15.03	0.56	20.22	5.48	€ 3,691	4.96	14.81	0.55	19.22	5.42	€ 3,549
		TS+eBI	1.61	2.72	0.03	4.30	0.32	€ 13,478	0.83	2.50	0.02	3.30	0.26	€ 12,899
		FR+eBI	2.50	3.54	0.26	5.77	2.72	€ 2,124	1.71	3.31	0.25	4.77	2.65	€ 1,798
		TS+FR+eBI	3.05	7.63	0.33	10.35	3.36	€ 3,077	2.27	7.40	0.32	9.35	3.30	€ 2,833

Table 15 - Full sensitivity analysis results for Sweden

			Versus no SBIs						Incremental versus baseline					
			Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	CER/QALY	Screening Cost (€m)	Policy cost (€m)	Hospital savings (€m)	Net cost (€m)	QALYs gained (,000s)	ICER/QALY
Sweden	Retraining every 5 years	Control	-51.39	0.63	0	-50.77	3.88	Dominates						
		TS	-45.11	24.13	0	-20.98	6.19	Dominates	6.28	23.50	0.00	29.79	2.31	€ 12,894
		FR	-37.50	23.98	0	-13.53	8.99	Dominates	13.89	23.35	0.00	37.24	5.11	€ 7,291
		eBI	-47.58	22.14	0	-25.45	5.28	Dominates	3.81	21.51	0.00	25.32	1.40	€ 18,068
		TS+FR	-34.58	27.09	0	-7.49	10.06	Dominates	16.81	26.46	0.00	43.28	6.18	€ 6,999
		TS+eBI	-46.07	26.08	0	-19.99	5.84	Dominates	5.32	25.46	0.00	30.78	1.96	€ 15,735
		FR+eBI	-41.77	19.79	0	-21.98	7.42	Dominates	9.63	19.16	0.00	28.79	3.54	€ 8,133
		TS+FR+eBI	-39.42	26.91	0	-12.51	8.28	Dominates	11.97	26.28	0.00	38.25	4.40	€ 8,691
	Retraining every 2 years	Control	-51.39	1.47	0.00	-49.92	3.88	Dominates						
		TS	-45.11	30.32	0.00	-14.79	6.19	Dominates	6.28	28.85	0.00	35.13	2.31	€ 15,210
		FR	-37.50	29.08	0.00	-8.42	8.99	Dominates	13.89	27.61	0.00	41.50	5.11	€ 8,125
		eBI	-47.58	28.02	0.00	-19.57	5.28	Dominates	3.81	26.55	0.00	30.36	1.40	€ 21,664
		TS+FR	-34.58	32.75	0.00	-1.83	10.06	Dominates	16.81	31.28	0.00	48.09	6.18	€ 7,778
		TS+eBI	-46.07	31.90	0.00	-14.17	5.84	Dominates	5.32	30.44	0.00	35.75	1.96	€ 18,280
		FR+eBI	-41.77	25.25	0.00	-16.52	7.42	Dominates	9.63	23.78	0.00	33.41	3.54	€ 9,437
		TS+FR+eBI	-39.42	33.93	0.00	-5.49	8.28	Dominates	11.97	32.46	0.00	44.43	4.40	€ 10,095