## Supplementary Figure 1 – Cost Effectiveness Acceptability Curve: Cost Utility Analysis

## Supplementary Figure 2 – Cost Effectiveness Acceptability Curve: Cost Effectiveness Analysis

**Supplementary Table 1: Potentially Inappropriate Prescribing Identification Criteria**

|  |  |  |
| --- | --- | --- |
| Criteria | Concern | Estimated prevalence in Ireland\* |
| PPI for peptic ulcer disease at full therapeutic dosage for>8 weeks | Earlier discontinuation or dose reduction for maintenance/ prophylactic treatment of peptic ulcer disease, oesophagitis or GORD indicated | 4.1- 16.7% |
| NSAID (>3 months) for relief of mild joint pain in osteoarthritis | Simple analgesics preferable and usually as effective for pain relief | 1.1 - 8.8% |
| Long-term (i.e. >1 month), long-acting benzodiazepines e.g. chlordiazepoxide, flurazepam, nitrazepam, chlorazepate and benzodiazepines with long-acting metabolites e.g. diazepam | Risk of prolonged sedation, confusion, impaired balance, falls | 3.0-9.1% |
| Any regular duplicate drug class prescription e.g. 2 concurrent opiates, NSAIDs, SSRIs, loop diuretics, ACE inhibitors. Excludes duplicate prescribing of drugs that may be required on a PRN basis e.g. Inhaled beta 2 agonists (long and short acting) for asthma or COPD, and opiates for management of breakthrough pain | Optimisation of monotherapy within a single drug class should be observed prior to considering a new class of drug | 2.2 – 6.0% |
| TCAs with an opiate or calcium channel blocker | Risk of severe constipation | 0.4-2.0% |
| Aspirin at dose >150 mg/day | Increased bleeding risk, no evidence for increased efficacy | 0.1-1.% |
| Theophylline as monotherapy for COPD/Asthma | Risk of adverse effects due to narrow therapeutic index | 0.6- 1.2% |
| Use of aspirin and warfarin in combination without histamine H2 receptor antagonist or PPI | high risk of GI bleeding | 0.3-1.1% |
| Doses of short-acting benzodiazepines, doses greater than: lorazepam 3 mg; oxazepam 60 mg; alprazolam 2 mg; temazepam 15 mg; and triazolam 0.25 mg | Total daily doses should rarely exceed the suggested maximums | 1.0-1.5% |
| Prolonged use (>1 week) of first generation antihistamines i.e. diphenydramine, chlorpheniramine, cyclizine, promethazine | Risk of sedation and anticholinergic side effects | <1.0% |
| Warfarin and NSAID together | Risk of GI bleeding | 0.7-1.7% |
| Calcium channel blockers with chronic constipation | May exacerbate constipation | <1.0% |
| NSAID with history of peptic ulcer disease or GI bleeding, unless with concurrent histamine H2 receptor antagonist, PPI or misoprostol | Risk of peptic ulcer relapse | <1.0% |
| Bladder antimuscarinic drugs with dementia | Risk of increased confusion, agitation | <1.0% |
| TCAs with constipation | May worsen constipation | <1.0% |
| Digoxin at a long-term dose>125 µg/day (with impaired renal function) | Increased risk of toxicity | <1.0%  <1.0% |
| Thiazide diuretic with a history of gout | May exacerbate gout | <1.0% |
| Glibenclamide (with type 2 diabetes mellitus) | Risk of prolonged hypoglycaemia | <1.0% |
| Aspirin with a past history of peptic ulcer disease without histamine H2 receptor antagonist or PPI | Risk of bleeding | <1.0% |
| Prochlorperazine or metoclopramide with Parkinsonism | Risk of exacerbating Parkinsonism | <1.0% |
| TCAs with dementia | Risk of worsening cognitive impairment | <1.0% |
| TCAs with glaucoma | Likely to exacerbate glaucoma | <1.0% |
| TCAs with cardiac conductive abnormalities | Pro-arrhythmic effects | <1.0% |
| Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis or osteoarthritis | Risk of major systemic corticosteroid side-effects | <1.0% |
| Bladder antimuscarinic drugs with chronic prostatism | Risk of urinary retention | <1.0% |
| NSAID with heart failure | Risk of exacerbation of heart failure | <1.0% |
| TCAs with prostatism or prior history of urinary retention | Risk of urinary retention | <1.0% |
| Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in COPD/Asthma | Unnecessary exposure to long-term side-effects systemic steroids | <1.0% |
| Bladder antimuscarinic drugs with chronic glaucoma | Risk of acute exacerbation of glaucoma | <0.01% |
| NSAID with SSRI | Increased risk of GI bleed | N/A |
| Bladder antimuscarinic drugs with chronic constipation | Risk of exacerbation of constipation | N/A |
| Prednisolone (or equivalent) > 3 months or longer without bisphosphonate | Increased risk of fracture | N/A |
| NSAID with ACE-inhibitor | Risk of kidney failure, particularly if presence of general arteriosclerosis, dehydration or concurrent use of diuretics | N/A |
| NSAID with diuretic | May reduce the effect of diuretics and worsen existing heart failure | N/A |

*Abbreviations – ACEI (angiotensin-converting-enzyme inhibitor); COPD (chronic obstructive pulmonary disease); GI (gastro-intestinal); NA (not available); GORD (gastro-oesophageal reflux disease); NSAID (Nonsteroidal anti-inflammatory drug); PPI (Proton Pump Inhibitor); PRN (Pro re nata, as needed); SSRI (Selective serotonin reuptake inhibitor); TCA (Tricyclic Anti-depressant)*

*\*Prevalence – the proportion of the study population with 1 or more potentially inappropriate medications from the literature*

**Supplementary Table 2 - Baseline characteristics of practices and patients.**

|  |  |  |
| --- | --- | --- |
| Characteristic | Intervention | Control |
| Practice factors | | |
| Number of practices (%) | 11 (52.4) | 10 (47.6) |
| GMS list size (%)   * 500 or less * 501- 1,500 * 1,501 and over | 1 (9.1)  3 (27.3)  7 (63.6) | 2 (20.0)  2 (20.0)  6 (60.0) |
| Practice with a manager | 8 (72.8) | 7 (70.0) |
| Location (%)   * Urban^ * Mixed | 8 (80.0)  3 (20.0) | 8 (72.7)  2 (27.3) |
| Mean number of GPs per practice (SD) | 4.1 (3.1) | 4.1(2.1) |
| Mean number of patients over 70 per practice (SD) | 712.1 (525.3) | 788.2 (987.2) |
| Median deprivation score† (IQR) | 0.5 (-0.3 to 1.6) | 1.4 (0.3 to 2.4) |
| Patient factors | | |
| Number of patients (%) | 99 (50.5) | 97 (49.5) |
| Male (%) | 55 (55.6) | 50 (51.5) |
| Marital status (%)   * Married * Widowed * Single | 56 (56.6)  26 (26.3)  14 (14.1) | 51 (53.1)  32 (33.3)  10 (10.4) |
| GMS card holder (SD) | 88 (88.9) | 95 (97.9) |
| Mean age (SD) | 77.1 (4.9) | 76.4 (4.8) |
| Mean number of repeat medications (SD) | 10.2 (4.5) | 9.5 (4.1) |

Figures are numbers (percentages) unless stated otherwise

^ Urban area: relatively small centre of population, with 5,000 or more residents

† Population weighted deprivation score for each practice - large values mean practices are situated in more socio-economically deprived areas

SD: Standard Deviation

IQR: Interquartile range

GMS: General Medical Services Scheme

**Supplementary Table 3 - Summary of OPTI-SCRIPT intervention and control groups**

|  |  |
| --- | --- |
| **Intervention** | The intervention consisted of:   1. Academic detailing with a pharmacist   One session (30 minutes) where a pharmacist visited the practice to discuss PIP, medicines review and the web-based pharmaceutical treatment algorithms   1. Medicines review with web-based pharmaceutical treatment algorithms. GPs were asked to conduct one review per patient using the web-based platform to guide them through the process. The GP was presented with the specific PIP drug(s) for each patient, and for each PIP drug, there was a treatment algorithm with the following structure:    1. The individual PIP with reason for concern    2. Alternative pharmacological and non-pharmacological treatment options    3. Background information (where relevant) 2. Patient information leaflets to give to patients during the review. Each leaflet: 3. Described the PIP and the reasons as to why it may be inappropriate 4. Outlined the alternative pharmacological and non-pharmacological therapies GPs may offer. |
| **Control** | Control practices delivered usual care. Usual care for public general medical services (GMS) patients allows GPs to give a prescription on a monthly or three monthly basis.  Control practices received simple patient-level PIP postal feedback in the form of a list summarizing the medication class to which the individual patient’s potentially inappropriate medication belonged.  Control practices did not receive an academic detailing visit or were not prompted to carry out medicines review with the individual patients. |

**Supplementary Table 4: Sensitivity Analysis 1: Regression Models Estimated Controlling for Treatment Arm Only**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Cost Analysis** | **Intervention** | | **Control** | |
| Healthcare Costs  (95% CIs) | 2700  (1771, 3628) | | 2501  (1628, 3374) | |
| Difference in Healthcare Cost  (95% CIs) | 203  (-991, 1397) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Effectiveness Analysis** | **Intervention** | | **Control** | |
| Number of PIPs  (95% CIs) | 0.606  (0.467, 0.745) | | 1.031  (0.868, 1.194) | |
| Difference in Number of PIPs  (95% CI) | -0.436  (-0.729, -0.143) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Effectiveness Analysis** | **Intervention** | | **Control** | |
| QALYs  (95% CIs) | 0.672  (0.585, 0 .761) | | 0.655  (0.592, 0 .718) | |
| Difference in QALYs (95% CI) | 0.011  (-0.108, 0.130) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| ICER per PIP avoided (€)  (95% CIs) | 465  (-2562, 4935) | | | |
| ICER per QALYs gained (€)  (95% CIs) | 18508  (-146806, 136726) | | | |
| **Probability that the Intervention is Cost Effective** | **PIP Avoided** | | **QALY Gained** | |
|  | **Threshold Value (λ)** | **P [CE]** | **Threshold Value (λ)** | **P [CE]** |
|  | **λ = €0** | 0.345 | **λ = €0** | 0.338 |
|  | **λ = €500** | 0.478 | **λ = €5,000** | 0.411 |
|  | **λ = €1,500** | 0.756 | **λ = €15,000** | 0.490 |
|  | **λ = €2,500** | 0.885 | **λ = €25,000** | 0.520 |
|  | **λ = €3,500** | 0.946 | **λ = €35,000** | 0.537 |
|  | **λ = €4,500** | 0.969 | **λ = €45,000** | 0.554 |

**Cost Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gamma variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm.

**PIP Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gaussian variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm.

**QALY Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gaussian variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm.

**Supplementary Table 5: Sensitivity Analysis 2: Imputed QALYs Analysis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Cost Analysis** | **Intervention** | | **Control** | |
| Healthcare Costs  (95% CIs) | 3075  (2704, 3446) | | 2668  (2297, 3040) | |
| Difference in Healthcare Cost  (95% CIs) | 407  (-357, 1170) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Effectiveness Analysis** | **Intervention** | | **Control** | |
| Number of PIPs  (95% CIs) | 0.627  (0.588, 0.666) | | 1.006  (0.967, 1.045) | |
| Difference in Number of PIPs  (95% CI) | -0.379  (-0.666, -0.092) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Effectiveness Analysis** | **Intervention** | | **Control** | |
| QALYs  (95% CIs) | 0.671  (0.625, 0.716) | | 0.657  (0.612, 0.703) | |
| Difference in QALYs (95% CI) | 0.032  (-0.032, 0.096) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| ICER per PIP avoided (€)  (95% CIs) | 1269  (-1400, 6302) | | | |
| ICER per QALYs gained (€)  (95% CIs) | 12748  (-136108, 187304) | | | |
| **Probability that the Intervention is Cost Effective** | **PIP Avoided** | | **QALY Gained** | |
|  | **Threshold Value (λ)** | **P [CE]** | **Threshold Value (λ)** | **P [CE]** |
|  | **λ = €0** | 0.143 | **λ = €0** | 0.130 |
|  | **λ = €500** | 0.278 | **λ = €5,000** | 0.253 |
|  | **λ = €1,500** | 0.654 | **λ = €15,000** | 0.527 |
|  | **λ = €2,500** | 0.845 | **λ = €25,000** | 0.656 |
|  | **λ = €3,500** | 0.926 | **λ = €35,000** | 0.732 |
|  | **λ = €4,500** | 0.951 | **λ = €45,000** | 0.764 |

**Incremental Cost Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gamma variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, baseline cost, number of GPs and practice location.

**Incremental PIP Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gaussian variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, number of GPs and practice location.

**Incremental QALY Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gaussian variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, baseline eq5d score, number of GPs and practice location. The multiple imputation included age, gender, practice, and treatment arm (at follow up only) and were estimated using predictive mean matching, based on M=5 imputed data sets. The analysis was undertaken using the MI estimate mixed and MI predict commands in Stata 13, which estimate the regression model on each of the imputed data sets and apply Rubin’s rules to generate the coefficients of interest.

**Supplementary Table 6: Sensitivity Analysis 3: PIPs Costs (Baseline Cost by 6 months + Follow Up Cost by 6 months)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Cost Analysis** | **Intervention** | | **Control** | |
| Healthcare Costs  (95% CIs) | 3158  (2779, 3536) | | 2718  (2339, 3096) | |
| Difference in Healthcare Cost  (95% CIs) | 440  (-347, 1227) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Effectiveness Analysis** | **Intervention** | | **Control** | |
| Number of PIPs  (95% CIs) | 0.627  (0.588, 0.666) | | 1.006  (0.967, 1.045) | |
| Difference in Number of PIPs  (95% CI) | -0.379  (-0.666, -0.092) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Effectiveness Analysis** | **Intervention** | | **Control** | |
| QALYs  (95% CIs) | 0.671  (0.625, 0.716) | | 0.657  (0.612, 0.703) | |
| Difference in QALYs (95% CI) | 0.013  (-0.016, 0.042) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| ICER per PIP avoided (€)  (95% CIs) | 1161  (-1271, 5748) | | | |
| ICER per QALYs gained (€)  (95% CIs) | 33021  (-253797, 447586) | | | |
| **Probability that the Intervention is Cost Effective** | **PIP Avoided** | | **QALY Gained** | |
|  | **Threshold Value (λ)** | **P [CE]** | **Threshold Value (λ)** | **P [CE]** |
|  | **λ = €0** | 0.128 | **λ = €0** | 0.147 |
|  | **λ = €500** | 0.262 | **λ = €5,000** | 0.186 |
|  | **λ = €1,500** | 0.582 | **λ = €15,000** | 0.312 |
|  | **λ = €2,500** | 0.826 | **λ = €25,000** | 0.438 |
|  | **λ = €3,500** | 0.915 | **λ = €35,000** | 0.516 |
|  | **λ = €4,500** | 0.948 | **λ = €45,000** | 0.572 |

**Cost Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gamma variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, baseline cost, number of GPs and practice location.

**PIP Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gaussian variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, number of GPs and practice location.

**QALY Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gaussian variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, baseline eq5d score, number of GPs and practice location.

**Supplementary Table 7: Sensitivity Analysis 4: PIPs Costs (Baseline Cost by 9 months + Follow Up Cost by 3 months)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Cost Analysis** | **Intervention** | | **Control** | |
| Healthcare Costs  (95% CIs) | 3196  (2814, 3578) | | 2743  (2361, 3125) | |
| Difference in Healthcare Cost  (95% CIs) | 453  (-344, 1250) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Effectiveness Analysis** | **Intervention** | | **Intervention** | |
| Number of PIPs  (95% CIs) | 0.627  (0.588, 0.666) | | 0.627  (0.588, 0.666) | |
| Difference in Number of PIPs  (95% CI) | -0.379  (-0.666, -0.092) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Effectiveness Analysis** | **Intervention** | | **Intervention** | |
| QALYs  (95% CIs) | 0.671  (0.625, 0.716) | | 0.671  (0.625, 0.716) | |
| Difference in QALYs (95% CI) | 0.013  (-0.016, 0.042) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| ICER per PIP avoided (€)  (95% CIs) | 1195  (-1231, 5503) | | | |
| ICER per QALYs gained (€)  (95% CIs) | 34001  (-408404, 390108) | | | |
| **Probability that the Intervention is Cost Effective** | **PIP Avoided** | | **QALY Gained** | |
|  | **Threshold Value (λ)** | **P [CE]** | **Threshold Value (λ)** | **P [CE]** |
|  | **λ = €0** | 0.121 | **λ = €0** | 0.155 |
|  | **λ = €500** | 0.248 | **λ = €5,000** | 0.193 |
|  | **λ = €1,500** | 0.589 | **λ = €15,000** | 0.307 |
|  | **λ = €2,500** | 0.809 | **λ = €25,000** | 0.419 |
|  | **λ = €3,500** | 0.903 | **λ = €35,000** | 0.504 |
|  | **λ = €4,500** | 0.948 | **λ = €45,000** | 0.570 |

**Cost Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gamma variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, baseline cost, number of GPs and practice location.

**PIP Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gaussian variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, number of GPs and practice location.

**QALY Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gaussian variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, baseline eq5d score, number of GPs and practice location.

**Supplementary Table 8: Sensitivity Analysis 5: Reduce Medication Costs by 50%**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Cost Analysis** | **Intervention** | | **Intervention** | |
| Healthcare Costs  (95% CIs) | 3059  (2486, 3631) | | 2595  (2077, 3114) | |
| Difference in Healthcare Cost  (95% CIs) | 416  (-354, 1185) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Effectiveness Analysis** | **Intervention** | | **Intervention** | |
| Number of PIPs  (95% CIs) | 0.627  (0.588, 0.666) | | 0.627  (0.588, 0.666) | |
| Difference in Number of PIPs  (95% CI) | -0.379  (-0.666, -0.092) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Effectiveness Analysis** | **Intervention** | | **Intervention** | |
| QALYs  (95% CIs) | 0.671  (0.625, 0.716) | | 0.671  (0.625, 0.716) | |
| Difference in QALYs (95% CI) | 0.013  (-0.016, 0.042) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| ICER per PIP avoided (€)  (95% CIs) | 1097  (-1097, 6014) | | | |
| ICER per QALYs gained (€)  (95% CIs) | 31190  (-481582, 436097) | | | |
| **Probability that the Intervention is Cost Effective** | **PIP Avoided** | | **PIP Avoided** | |
|  | **Threshold Value (λ)** | **Threshold Value (λ)** | **Threshold Value (λ)** | **Threshold Value (λ)** |
|  | **λ = €0** | 0.145 | **λ = €0** | 0.129 |
|  | **λ = €500** | 0.286 | **λ = €5,000** | 0.164 |
|  | **λ = €1,500** | 0.646 | **λ = €15,000** | 0.284 |
|  | **λ = €2,500** | 0.835 | **λ = €25,000** | 0.417 |
|  | **λ = €3,500** | 0.924 | **λ = €35,000** | 0.507 |
|  | **λ = €4,500** | 0.956 | **λ = €45,000** | 0.569 |

**Cost Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gamma variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, baseline cost, number of GPs and practice location.

**PIP Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gaussian variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, number of GPs and practice location.

**QALY Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gaussian variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, baseline eq5d score, number of GPs and practice location.

**Supplementary Table 9: Sensitivity Analysis 6: OPTI-SCRIPT Intervention Cost by 100%**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Cost Analysis** | **Intervention** | | **Control** | |
| Healthcare Costs  (95% CIs) | 3149  (2776, 3524) | | 2655  (2281, 3030**)** | |
| Difference in Healthcare Cost  (95% CIs) | 494  (-284, 1272) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Effectiveness Analysis** | **Intervention** | | **Control** | |
| Number of PIPs  (95% CIs) | 0.627  (0.588, 0.666) | | 1.006  (0.967, 1.045) | |
| Difference in Number of PIPs  (95% CI) | -0.379  (-0.666, -0.092) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Effectiveness Analysis** | **Intervention** | | **Control** | |
| QALYs  (95% CIs) | 0.671  (0.625, 0.716) | | 0.657  (0.612, 0.703) | |
| Difference in QALYs (95% CI) | 0.013  (-0.016, 0.042) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| ICER per PIP avoided (€)  (95% CIs) | 1304  (-1077, 5958) | | | |
| ICER per QALYs gained (€)  (95% CIs) | 37093  (-366020, 304909) | | | |
| **Probability that the Intervention is Cost Effective** | **PIP Avoided** | | **QALY Gained** | |
|  | **Threshold Value (λ)** | **P [CE]** | **Threshold Value (λ)** | **P [CE]** |
|  | **λ = €0** | 0.105 | **λ = €0** | 0.120 |
|  | **λ = €500** | 0.221 | **λ = €5,000** | 0.150 |
|  | **λ = €1,500** | 0.550 | **λ = €15,000** | 0.277 |
|  | **λ = €2,500** | 0.782 | **λ = €25,000** | 0.410 |
|  | **λ = €3,500** | 0.895 | **λ = €35,000** | 0.508 |
|  | **λ = €4,500** | 0.938 | **λ = €45,000** | 0.567 |

**Cost Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gamma variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, baseline cost, number of GPs and practice location.

**PIP Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gaussian variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, number of GPs and practice location.

**QALY Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gaussian variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, baseline eq5d score, number of GPs and practice location.

**Supplementary Table 10: Sensitivity Analysis 7: Excluding PIP Costs**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Cost Analysis** | **Intervention** | | **Control** | |
| Healthcare Costs  (95% CIs) | 3021  (2418, 3624) | | 2528  (1982, 3074) | |
| Difference in Healthcare Cost  (95% CIs) | 336  (-857, 1529) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Effectiveness Analysis** | **Intervention** | | **Control** | |
| Number of PIPs  (95% CIs) | 0.627  (0.588, 0.666) | | 1.006  (0.967, 1.045) | |
| Difference in Number of PIPs  (95% CI) | -0.379  (-0.666, -0.092) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| **Effectiveness Analysis** | **Intervention** | | **Control** | |
| QALYs  (95% CIs) | 0.671  (0.625, 0.716) | | 0.657  (0.612, 0.703) | |
| Difference in QALYs (95% CI) | 0.013  (-0.016, 0.042) | | | |
|  | **INCREMENTAL ANALYSIS**  (Intervention versus Control) | | | |
| ICER per PIP avoided (€)  (95% CIs) | 888  (-3494, 7399) | | | |
| ICER per QALYs gained (€)  (95% CIs) | 25251  (-359505, 375246) | | | |
| **Probability that the Intervention is Cost Effective** | **PIP Avoided** | | **QALY Gained** | |
|  | **Threshold Value (λ)** | **P [CE]** | **Threshold Value (λ)** | **P [CE]** |
|  | **λ = €0** | 0.278 | **λ = €0** | 0.288 |
|  | **λ = €500** | 0.402 | **λ = €5,000** | 0.327 |
|  | **λ = €1,500** | 0.646 | **λ = €15,000** | 0.415 |
|  | **λ = €2,500** | 0.800 | **λ = €25,000** | 0.474 |
|  | **λ = €3,500** | 0.881 | **λ = €35,000** | 0.536 |
|  | **λ = €4,500** | 0.924 | **λ = €45,000** | 0.590 |

**Cost Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gamma variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, baseline cost, number of GPs and practice location.

**PIP Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gaussian variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, number of GPs and practice location.

**QALY Analysis**: Estimated by a generalised estimating equation regression model, assuming a Gaussian variance function, an identity link function and an exchangeable correlation structure, controlling for treatment arm, age, gender, baseline number of PIP drugs, baseline eq5d score, number of GPs and practice location.

**Supplementary Table 11: Univariate statistical analysis, using independent t-tests, to compare mean resource use costs at baseline and follow up**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Intervention (N=99)**  *Mean (SD)* | **Control (N=97)**  *Mean (SD)* |  | |
| **Resource item** | **Cost (€)** | **Cost (€)** | ***t-test statistic*** | ***p-value*** |
| **Baseline**  PIP  GP Visits  GP Visits: Script Only  Practice Nurse Visits  Out of Hours GP Visits  Outpatient Visits  Day Case Admission  Inpatient Admission  A&E Visits | 230 (172)  434 (203)  143 (180)  21 (32)  10 (36)  355 (351)  49 (175)  688 (2705)  34 (113) | 302 (186)  432 (260)  123 (151)  19 (22)  10 (34)  327 (327)  79 (239)  660 (2489)  26 (80) | t = 2.8121  t = -0.0472  t = -0.8330  t = -0.7008  t = 0.0624  t = -0.5722  t = 0.9997  t = -0.0738  t = -0.5346 | 0.0054  0.9624  0.4059  0.4843  0.9503  0.5679  0.3187  0.9412  0.5936 |
| **Follow Up**  PIP  GP Visits  GP Visits: Script Only  Practice Nurse Visits  Out of Hours GP Visits  Outpatient Visits  Day Case Admission  Inpatient Admission  A&E Visits | 93 (131)  398 (225)  112 (131)  24 (31)  7 (24)  343 (277)  119 (364)  1497 (4430)  39 (117) | 200 (217)  405 (242)  110 (128)  19 (29)  7 (19)  342 (314)  101 (312)  1270 (4001)  38 (117) | t = 4.1630  t = 0.2044  t = -0.0936  t = -1.0573  t = -0.1196  t = -0.0266  t = -0.3606  t = -0.3700  t = -0.0959 | 0.0000  0.8383  0.9255  0.2917  0.9049  0.9788  0.7188  0.7118  0.9237 |