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Economic impact of potentially inappropriate prescribing and related adverse events in older people: a cost-utility analysis using Markov models

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Abstract

Objectives: To determine the economic impact of three drugs commonly involved in potentially inappropriate prescribing (PIP) in adults aged ≥65 years, including their adverse effects (AEs): long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, and proton pump inhibitors (PPIs) at maximal dose; to assess cost-effectiveness of potential interventions to reduce PIP of each drug.

Design: Cost-utility analysis. We developed Markov models incorporating the AEs of each PIP, populated with published estimates of probabilities, health system costs (in 2014 euro), and utilities.

Participants: A hypothetical cohort of 65 year olds analysed over 35 one-year cycles with discounting at 5% per year.

Outcome measures: Incremental cost, Quality-Adjusted Life Years (QALYs) and incremental cost-effectiveness ratios with 95% credible intervals (CIs, generated in probabilistic sensitivity analysis) between each PIP and an appropriate alternative strategy. Models were then used to evaluate the cost-effectiveness of potential interventions to reduce PIP for each of the three drug classes.

Results: All three PIP drugs and their AEs are associated with greater cost and fewer QALYs compared to alternatives. The largest reduction in QALYs and incremental cost was for benzodiazepines compared to no sedative medication (€3,470, 95%CI €2,434, €5,001; -0.07 QALYs, 95%CI -0.089, -0.047), followed by NSAIDs relative to paracetamol (€806, 95%CI €415, €1,346; -0.07 QALYs, 95%CI -0.131, -0.026), and maximal dose PPIs compared to maintenance dose PPIs (€989, 95%CI -€69, €2,127; -0.01 QALYs, 95%CI -0.029, 0.003). For interventions to reduce PIP, at a willingness-to-pay of €45,000 per QALY, targeting NSAIDs would be cost-effective up to the highest intervention cost per person of €1,971. For benzodiazepine and PPI interventions, the equivalent cost was €1,480 and €831 respectively.

Conclusions: Long-term benzodiazepine and NSAID prescribing are associated with significantly increased costs and reduced QALYs. Targeting inappropriate NSAID prescribing appears to be the most cost-effective PIP intervention.

Strengths and limitations of this study

- Novel application of economic modelling methods to assess three common types of potentially inappropriate prescribing.
- Analysis included the principal adverse effects of each potentially inappropriate medication.
- Uncertainty of estimates was quantified using probabilistic sensitivity analysis.
- The study did not consider differences in adverse event risk among individual drugs within each class, or heterogeneity in economic impact among patient sub-groups.

Introduction

Potentially inappropriate prescribing (PIP), the use of medicines where the risks outweigh the benefits, is prevalent among adults aged ≥65 years, particularly in individuals taking multiple medicines or with multiple chronic conditions.[1,2] Several explicit measures of PIP have been developed, including Beers criteria and the Screening Tool for Older Person's Prescriptions (STOPP), and while their relationship with some patient outcomes has been evaluated, the effect on the wider health system is also important to consider, in particular on healthcare costs.[3] The use of potentially inappropriate medicines can have an impact on health care costs due to pharmaceutical expenditure relating to the prescriptions themselves and due to managing the adverse events which may result. In two systematic reviews, one of studies assessing the STOPP criteria and another on the economic impact of inappropriate drug prescribing more generally, only direct medication costs of PIP drugs were assessed.[3,4]

Furthermore, in only assessing the direct cost of inappropriate drugs, the economic consequences of appropriate prescriptions used as an alternative to PIP medicines are not accounted for.[4,5] The costs of managing any resulting adverse events have yet to be quantified for PIP as a whole, and have only been assessed for individual medication classes to date, such as benzodiazepines and NSAIDs.[6–8] The economic impact of PIP is important when considering whether interventions to reduce PIP are an efficient use of resources and health professionals' time relative to other competing priorities. Few economic evaluations of trials to optimise prescribing for older people have been published,[3,9,10] which may limit implementation of such interventions by decision-makers, given scarce healthcare resources.

Based on prevalence estimates from a recent analysis in Ireland,[2] the aim of this study is to estimate and compare the economic impact of three common indicators of PIP: long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, and maximal dose proton pump inhibitors (PPIs). Specifically, we compare each of the three PIP drugs to a more appropriate treatment using Markov models to assess differences in quality and quantity of life and cost to the health system. We then apply the models to explore the cost-effectiveness of potential interventions based on recently published trials targeting these PIP drugs.

Methods

Markov models

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement was used in the design and reporting of this research (included as Appendix 1).[11] A Markov model was developed for each of the included PIP drugs using TreeAge Pro 2015 (TreeAge Software Inc., Williamstown, MA). This type of decision-analytic model was chosen to allow for time dependency, a particularly important consideration in the context of older people on long-term medicines.[12] The base case analysis used a target population of hypothetical 65 year olds who were community-dwelling in Ireland and had no current or previous adverse events relating to these PIP drugs. A health system perspective was used over a time horizon of 35 years (i.e. to age 100) with a half cycle correction.[13] In each of the three cases, the PIP strategy was compared to an alternative strategy, selected as an appropriate therapeutic option instead of the PIP drug (with respect to effectiveness and safety). The models incorporated the principal adverse drug events relating to each PIP (see Table 1). The primary outcomes evaluated were costs and quality-adjusted life years (QALYs). Life years (LYs) and number/rate of adverse events were also quantified as secondary outcomes. A discount rate for costs, QALYs, and LYs was applied at 5% per annum, and was varied from 0% to 6% in sensitivity analysis, in line with guideline recommendations.[14]

This cohort consisted of healthy community-dwelling older people, therefore in each model, all individuals start in a 'Well' state (see Figure A1 in Appendix 2 for state transition diagrams for each model). In subsequent cycles, individuals could transition to other states as a result of adverse events relating to the potentially inappropriate medicines of interest. Individuals remain in the adverse event state for one cycle unless they have a further adverse event in the subsequent cycle, and otherwise they transition to the post-event state (if applicable) or the relevant 'Well' state. Mortality attributable to adverse events and background age-related mortality were included. An in-depth description of the structure and transitions for each model is included in section 1 of Appendix 2. The models were populated with parameter estimates (see Table A1) derived from published sources which are described in detail in section 2 of Appendix 2.

Model inputs

Transition probabilities

Probabilities of transitions between states for the three models were taken from published literature sources which reported rates or probabilities of the adverse events of interest.

Population-based epidemiological studies with study samples representative of older community-dwelling adults were used, whenever possible, reflecting the baseline rate of adverse events for individuals in the appropriate alternative models (see Table A1). In the PIP models, a measure of the relative risk associated with the PIP drug was applied to the baseline probability for each adverse event. These were taken from meta-analyses of randomised controlled trials for NSAIDs,[15–17] meta-analyses of observational studies for benzodiazepines,[18,19] and for PPIs from a meta-analysis of observational studies,[20] and a single observational study.[21]. Annual probability of death from all causes was based on age-specific population rates for 2014 from the Central Statistics Office (CSO).[22] Excess mortality estimates following adverse events were taken from observational studies,[23–28] and were assumed to be independent of PIP exposure (i.e. the same post-event mortality was applied in both PIP and alternative scenarios).

Utility values

To increase comparability between the models, the same baseline utility value was applied to all 'Well' or no event health states. The source of these values were UK population norms for the EQ-5D visual analogue scale for people aged 65-74 and 75 years and over.[29] Utility decrements or disutilities, the annual reduction in utility due to an adverse event were taken from previous economic evaluations or studies that derived these values from patients with the relevant adverse event. These were subtracted from this baseline utility to give the utility value for each state.

Costs

Each state was assigned a cost reflecting the average annual costs to the Irish health system for a patient in that health state, relating to hospital inpatient care, general practitioner, out-patient department, and emergency department visits, medicines, and long-term (residential) care. Costs in euro from 2014 were used, and where not available historical costs were inflated using the applicable Consumer Price Index Health sub index from the CSO. In the case of *C. difficile* infection, international estimates of attributable costs were inflated to 2014 costs using the CPI from the origin country, and were then converted to Irish costs using the Purchasing Power Parity index.[14] Additional healthcare use attributable to adverse events was identified from published studies and Irish unit costs were assigned.[30]

Assumptions

It was assumed that prescribed medicines were consumed (i.e. full adherence) and over-the-counter use was not included in the models. Health states only related to the adverse events of

each PIP, so it was assumed that there was no significant differences in efficacy between each PIP and the appropriate alternative, and no significant adverse effects of the appropriate alternative. In the NSAID model, following an adverse event, it was assumed that individuals would be switched to an appropriate alternative. In the other models, it was assumed that individuals remained on therapy regardless of adverse events, due to unlikely attribution of the adverse events in the case of PPIs and dependence and withdrawal effects in the case of benzodiazepines. The effect of this assumption was assessed in structural sensitivity analysis.

Analytic methods

Economic impact of PIP relative to appropriate alternatives

Model structures were assessed for face validity by the research team and models were cross-validated by comparison to other published models concerning these therapeutic areas.[31] Models were validated by double-programming in Microsoft Excel 2010 (Microsoft Corp., Redmond, WA) to detect structural or coding errors, and extreme value testing and comparison of cohort traces between TreeAge Pro and Excel were also conducted.[31] The models programmed in Excel are available from https://doi.org/10.6084/m9.figshare.5818251.v1, and TreeAge Pro model structures are included as Figures A2-4 in section 4, Appendix 2.

Base case models were run for the PIP and appropriate scenarios using point estimates for transition probabilities, costs, and utilities (as shown in Table A1 in Appendix 2) and results are presented as mean differences in costs, QALYs, and LYs. An incremental cost-effectiveness ratio (ICER) was also calculated for each PIP, indicating the expected additional cost per additional QALY in the PIP scenario relative to the appropriate alternative scenario. Differences in the total number of adverse events for the PIP scenario compared to the appropriate scenario were also determined. Uncertainty associated with imprecision of the parameter inputs was incorporated into the model using probabilistic sensitivity analysis (PSA) to allow 95% credible intervals (CIs) to be fitted (see Appendix 2, section 3 for further details). The impact of varying specific parameter inputs, including costs and discount rates, was assessed in one-way deterministic sensitivity analyses.[14]

Cost-effectiveness of potential interventions

In the second stage of the analysis, each model was used to evaluate the cost-effectiveness of a potential intervention to reduce prescribing of each PIP drug by switching patients to the more appropriate alternative. This analysis was in the form of a value of implementation analysis,[32] and a new decision was framed between implementing an intervention to reduce PIP or usual care, as

illustrated for NSAIDs in Figure A5 in Appendix 2. The intervention was delivered once at the beginning of the model to all individuals on a long-term NSAID and resulted in a proportion of these people being switched to paracetamol for the duration of the model time horizon. The intervention cost per person and effectiveness (i.e. the relative reduction in the proportion on a long-term NSAID) were varied to determine circumstances in which the intervention would be preferred to no intervention at a willingness-to-pay or cost-effectiveness threshold of €45,000/QALY (the conventionally used threshold in Ireland),[14] as well as thresholds of €20,000/QALY and €0/QALY. These results were plotted and this was then repeated for benzodiazepine and PPIs. Threshold analysis was conducted using effectiveness estimates from recent primary care trials targeting these PIP drugs which have no published economic evaluation to date to determine maximal costs at which each medicines optimisation intervention would be cost-effective (see section 5 of Appendix 2 for a description of these trials).[33–35]

Patient involvement

Patients were not involved in the conception, design, or conduct of this research.

Results

Economic impact of PIP relative to appropriate alternatives

Based on the study parameters used (Table A1), for all three models the PIP scenarios were dominated by the appropriate treatment scenarios (i.e. they generated higher costs and fewer QALYs). The incremental costs and QALYs were largest in the benzodiazepine model, where being on the PIP drug generated an average of €3,470 higher costs and 0.07 fewer QALYs per patient compared to the appropriate alternative scenario (Table 2). For costs, this was followed by patients on a long-term maximal dose PPI relative to those on a maintenance dose and then being on long-term NSAIDs compared to paracetamol. The QALY loss in the NSAID model was 0.07 QALYs and 0.01 QALYs in the PPI model. Section 6 of Appendix 2 provides more detailed results, including total costs and QALYs per model (Table A2) and excess adverse events in the PIP scenarios relative to the appropriate alternative scenarios (Table A3). Uncertainty in the outcomes is illustrated in Figure 1 showing the distribution of cost and QALY differences for each model in the PSA. The 95% CIs generated from the PSA showed incremental costs and QALY losses were statistically significant for the NSAID (95% CI €415, €1,346 costs; -0.131, -0.026 QALYs) and benzodiazepine models (95% CI €2,434, €5,001 costs; -0.089, -0.047 QALYs). For the PPI model, the difference in costs and QALYs between maximal dose and maintenance dose prescribing was not statistically significant (95% CI -€69, €2,127 costs; -0.029, 0.003 QALYs).

In one-way deterministic sensitivity analysis, the PIP scenario was still dominated by the appropriate alternative scenario in each model across the range of values for the investigated parameters and the rankings of the models by incremental costs and QALYs did not change (see Table A4 in Appendix 2). Altering the NSAID model structure to assume no switch from the PIP drug to paracetamol after an adverse event (i.e. if patients remained on a long-term NSAID regardless of adverse events occurrence, consistent with the benzodiazepine and PPI models) resulted in a larger cost difference (€1,494, 95% CI €756, €2,493) and QALY difference (-0.11 QALYs, 95% CI -0.042, -0.203) between the PIP and appropriate scenarios. The distribution of cost and QALY estimates under this assumption is plotted in Figure A6 in Appendix 2.

Cost-effectiveness of potential interventions

Applying these models to determine the cost-effectiveness of potential interventions, the relationship between intervention cost, effectiveness and preferred option (intervention or usual care i.e. no intervention) is represented graphically for each PIP drug in Figure 2. Additionally, see

Figure A7 in Appendix 2 for an example interpretation of these plots. Taking estimates of effectiveness from recently published trials targeting these PIP drugs,[33–35] an intervention which reduces potentially inappropriate NSAID use by 49.8% would be cost-effective up to a cost of €1,971 per person at a CE threshold of €45,000. For an intervention that resulted in 23% discontinuation among benzodiazepine users, the corresponding threshold cost would be €1,480 and for a 55% reduction in potentially inappropriate PPI use it would be €831 (Table 3). The rank order of these potential interventions depended on the CE threshold used. Taking the extreme case of a CE threshold of €0 per QALY (i.e. willing to pay nothing additional for any QALY gain), cost-effectiveness would be achieved for interventions targeting NSAIDs, benzodiazepines, and PPIs up to costs per patient of €401, €798, and €544 respectively (Table 3).

Discussion

For the three PIP Markov models considered, the costs were greater and there were fewer QALYs where the potentially inappropriate medicine was prescribed compared to an appropriate alternative strategy (Table 2). For PPIs, the differences between the PIP and appropriate alternative did not reach statistical significance due to uncertainty in the risk of adverse events attributable to using maximal doses relative to maintenance doses (Figure 1). Of the three PIP drugs considered in this study, benzodiazepines for greater than four weeks compared to no sedative medicine had the greatest cost and QALY impact per patient (Table 2). In the evaluation of the cost-effectiveness of reducing PIP of these drugs, targeting long-term NSAIDs prescribing would be most cost-effective due to the published effectiveness of the intervention that was evaluated, though the ranking depended on the CE threshold used (Table 3).

Context of the literature

No other studies appear to have assessed the economic impact of PIP defined by STOPP beyond direct costs of medicines.[3] Several studies have quantified the costs of adverse events relating to drug classes included in this analysis, although in different settings.[36] For NSAIDs, the costs associated with no gastroprotection among older patients with peptic ulcer disease in the UK, the excess costs of GI injury among older US Medicaid patients, and the comparative costs of harm due to different NSAIDs have been evaluated.[6,9,37] Benzodiazepine drug interactions, although not potentially inappropriate benzodiazepine prescribing, were associated with significantly increased healthcare costs in a regression analysis of older patients,[7] while a further case-control study considered the attributable fall-related hospitalisation costs.[38] An economic modelling study comparing benzodiazepines to cognitive behavioural therapy or no treatment among older adults with insomnia, which although only considering a time horizon of one year, also found substantial falls-related costs associated with sedative drug use.[8] While decision tree analysis has been used to evaluate different PPI treatment strategies, including dose reduction, to manage oesophagitis,[39] the economic impact of adverse events or inappropriate prescribing of PPIs has not been evaluated.

A number of studies have reported the effectiveness of interventions to address appropriateness of prescribing in older people in primary care, but few economic evaluations have been published.[3,10] The PINCER intervention in English GP practices was cost-effective in both the in-trial economic evaluation and the model-based cost-utility analysis over a 5-year time horizon beyond the trial.[9,40] However there was uncertainty in the model-based results due to a lack of

precise estimates of harm in the published literature for some of the prescribing/monitoring errors targeted.[9] An older study of clinical pharmacist advice to older US veterans on five or more medicines and their doctors reported a cost of $7.50-30 (€12-48) per patient per unit improvement in the Medication Appropriateness Index.[41] Other published economic evaluations have focussed on appropriate prescribing of only specific drug classes, such as benzodiazepines,[42,43] psychiatric medicines,[44,45] or cardiovascular medicines.[46] Of all of these interventional studies, only the PINCER trial conducted a model-based economic evaluation presenting results as an ICER (i.e. cost per QALY). Several recent trials of primary care interventions have successfully reduced PIP drugs. The OPTI-SCRIPT intervention involved academic detailing by a pharmacist and a computer decision support system for GPs in Ireland and resulted in a reduction in PIP, and in particular in long-term use of PPIs at maximal dosage.[33] The Scottish DQIP intervention employing education, informatics and incentives to assist GPs reviewing older patients' prescribing effectively decreased high-risk prescribing of NSAIDs and other medicines, and reduced the rate of hospitalisation for GI bleeding and heart failure.[34] Finally, the EMPOWER trial demonstrated that a patient empowerment intervention delivered through Canadian community pharmacies results in greater discontinuation of benzodiazepines than standard care.[35] The cost-effectiveness of these interventions has yet to be demonstrated through published economic evaluations, and hence this study illustrates the use of Markov models to assess the cost-effectiveness of reducing PIP and the resulting adverse events.

Strengths and limitations

This is the first study to quantify the economic impact of PIP in older people, considering not just the medication cost but also the adverse consequences. The use of Markov models allowed for available evidence on harm relating to PIP criteria from the published literature to be combined. The analysis also incorporated uncertainty in these estimates and a number of model validation steps were conducted. This study directly compared three types of suboptimal prescribing with distinct adverse effects on a common scale of costs and QALYs. Similarly it illustrates that the cost-effectiveness of potential interventions to improve prescribing in older people can be assessed using Markov modelling to capture the long-term consequences of medicines optimisation.

This study has several limitations. Only the principal adverse effects of each PIP were included to reduce the complexity and increase transparency of the models. A number of model assumptions were applied to address this study's aim. Firstly, as the STOPP criteria refer to drug classes, we used pooled estimates for each class for the risk of adverse effects to provide the average economic

impact of each PIP, and heterogeneity within drug classes was beyond the scope of this study. Similarly we did not consider strategies that modify risks, such as gastroprotection with NSAIDs to prevent GI adverse events with NSAIDs. Secondly the cohort under consideration were 65 year olds, assumed to be continuous users of each PIP, and in the intervention evaluation, the reduction in PIP was assumed to be sustained over the full time horizon. In reality, patients may spend some time exposed and unexposed, however, these assumptions allowed the overall effects of each PIP to be compared. The analysis was performed on a cohort basis to assess the average costs and effects, which does not reflect the variability of these outcomes among individuals, where some patients may incur large costs and have a greater reduction in QALYs. Heterogeneity was also not considered, as the research did not aim to evaluate how the economic impact may vary among patient subgroups. This analysis focussed only on adverse effects of prescribing deemed to be potentially inappropriate, however appropriate alternative were selected on the basis of similar effectiveness and limited adverse effects.

Implications for policy and practice

Trial-based economic evaluations may not always be informative for policy-maker decisions due to, for example, relevant comparators not being included, an insufficient time horizon, or measurement of intermediary endpoints only, such as serum cholesterol or process measures like PIP, rather than final outcomes.[30] Modelling approaches can overcome these weaknesses, by allowing all relevant evidence to be synthesised, incorporating alternative treatments not directly compared in a trial, and extrapolating beyond the duration of the trial to assess long-term outcomes.[12] Adoption of economic modelling approaches could increase the number of informative economic evaluations of prescribing safety interventions, such as in the PINCER trial.[9] Such methods may be particularly useful in evaluating services to improve other aspects of medicines use where the benefits may not manifest during the period of a trial, for example, an intervention to improve adherence to medicines for chronic conditions.[47] Future trials of new or expanded services should conduct robust economic evaluations, including long-term consequences, to inform policy-makers' decisions on implementation and funding allocation. Cost-utility analyses presenting results as cost per QALY are most informative, allowing policy-makers to compare interventions and make funding decisions across therapeutic domains. Model-based approaches, as illustrated here, are an effective method to produce these estimates and evaluate interventions which affect outcomes across physiological systems.

Prescribing of potentially inappropriate medicines has significant economic implications and interventions to reduce PIP are likely to be cost-effective if implemented into primary care for older people. The 95% CIs for differences in costs and QALYs in the PPI model both included zero, which, similar to the PINCER trial, was due to uncertainty relating to the adverse effects.[9] This indicates more information is needed on the safety of maximal compared to maintenance doses,[48] and therefore these results should not deter efforts to deprescribe PPIs where their use is potentially inappropriate.[2,33] As illustrated in Table 3, the CE threshold being used by policy-makers (i.e. the value they are willing to pay for a QALY) can influence which interventions are funded - placing a greater monetary value on each QALY will favour interventions which improve quality and quantity of life over those that provide benefit by reducing healthcare costs. While an explicit CE threshold exists for new drugs in the Irish health system, it is less clear whether the same applies to non-pharmaceutical interventions, such as those to improve prescribing.[49] It may be that a lower CE threshold applies to these, for instance where no additional funding is available for medicines optimisation services and only cost-saving interventions are acceptable to decision-makers. Using a different CE threshold may alter healthcare decisions and potentially result in less net benefit for patients across the health system.[49]

Conclusions

Potentially inappropriate prescribing of benzodiazepines and NSAIDs carry a statistically significant cost, to both the health system and patients, and there is an economic case for research on implementing effective interventions to improve prescribing for older people. Maximal dose PPI use is highly prevalent and so further studies should consider whether continuing maximal dose PPI is associated with increased risks compared to maintenance dose prescribing in order to establish whether targeting this is an efficient use of resources. Future research should also evaluate in which patient subgroups does inappropriate medication use have the greatest economic impact and thus, for which patients would prescribing optimisation interventions be most cost-effective.

Data sharing: Markov models coded in Microsoft Excel are available at https://doi.org/10.6084/m9.figshare.5818251.v1 and data inputs are included in the technical appendix (Appendix 2).

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Transparency statement: FM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Figures

Figure 1 Incremental costs and utilities for PIP compared to appropriate from probabilistic sensitivity analysis for each model (northwest quadrant)

Figure 2 Cost and effectiveness at which interventions would be cost-effective at a cost-effectiveness threshold of €45,000 per QALY for a) benzodiazepine, b) PPI, and c) NSAID models

Tables

Table 1 Description of included criteria from the Screening Tool for Older Persons' Prescriptions (STOPP)

Potentially inappropriate prescription	Comparator	Prevalence [2]	Adverse events represented
NSAID >3 months	Paracetamol	4.1%	Dyspepsia Gastrointestinal bleed Myocardial infarction
Benzodiazepine >4 weeks	No sedative medication	4.3%	Hip fracture Other fall injuries
PPI maximal dose >8 weeks	Maintenance dose PPI	23.6%	Hip fracture *Clostridium difficile* infection

Table 2 Cost, effect, and ICER outputs for PIP compared to appropriate scenarios for each model

Model	Incremental Cost (€)	Incremental QALYs	ICER (€ per QALY)	Incremental LYs
NSAID model	806	-0.07	-11,511	-0.08
Benzodiazepine model	3,470	-0.07	-52,672	-0.04
PPI model	989	-0.01	-85,279	-0.02

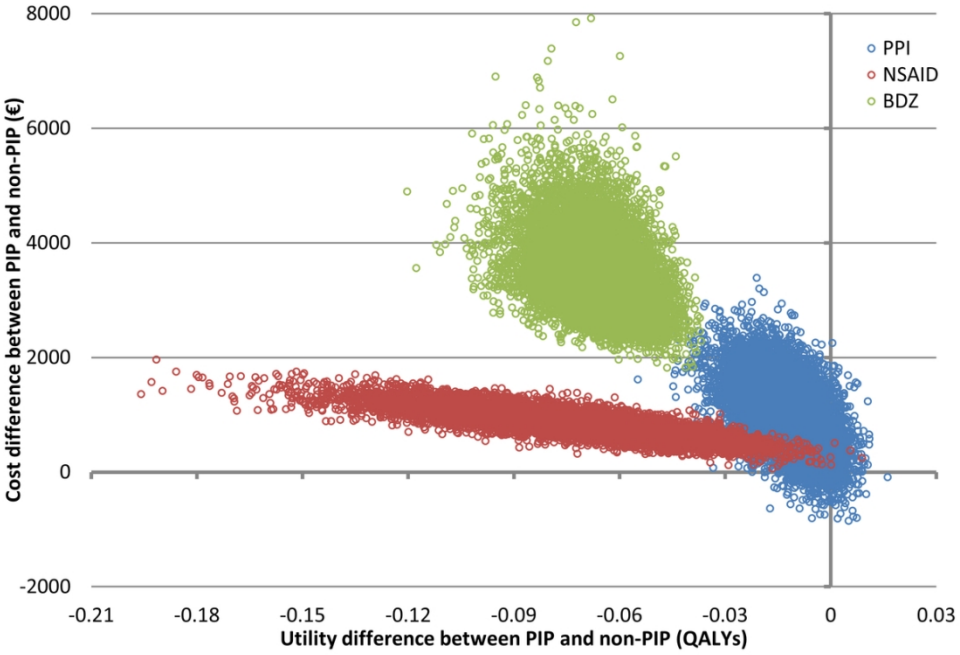
Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; QALYs, quality-adjusted life years.

Table 3 Threshold values across cost-effectiveness thresholds for intervention cost at levels of effectiveness from published trials[a]

	Threshold cost (€) at published intervention effectiveness[a]		
WTP (€ per QALY)	**NSAIDs**	**Benzodiazepines**	**PPIs**
0	401	798	544
20,000	1099	1101	671
45,000	1971	1480	831

Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; QALY, quality-adjusted life year; WTP, willingness-to-pay.

[a] Effectiveness estimates used were 0.498, 0.23, and 0.55 for NSAID,[34] benzodiazepine,[35] and PPI[33] interventions respectively.



Incremental costs and utilities for PIP compared to appropriate from probabilistic sensitivity analysis for each model (northwest quadrant)

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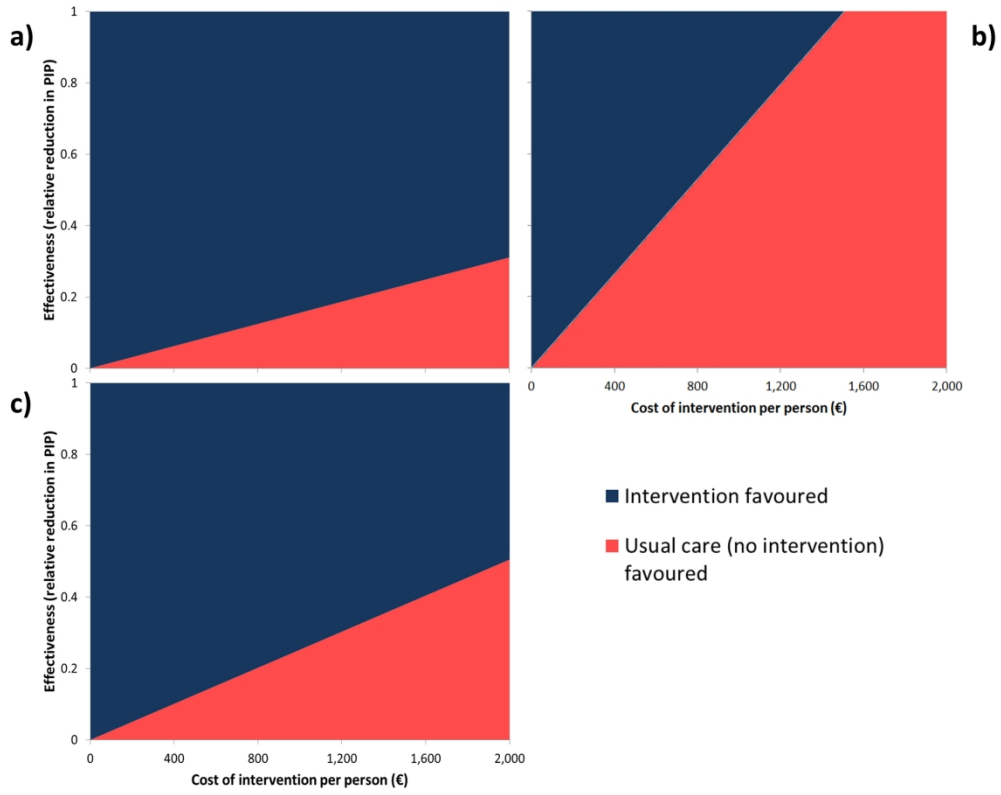

Cost and effectiveness at which interventions would be cost-effective at a cost-effectiveness threshold of €45,000 per QALY for a) benzodiazepine, b) PPI, and c) NSAID models

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Section/item	Item No	Recommendation	Reported on page No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 4, paragraph 1
		Present the study question and its relevance for health policy or practice decisions.	Page 4, paragraphs 2-3
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 5, paragraph 1
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 5, paragraph 1
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 5, paragraph 1
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 5, paragraph 1 and Table 1
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5 paragraph 1
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 5, paragraph 1
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 5, paragraph 1 and Page 6, paragraphs 2-3
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Technical appendix, section 2.1
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Page 6, paragraph 2 and Technical appendix, section 2.3
Estimating resources and costs	13a	*Single study-based economic evaluation:*Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate	Page 6, paragraph 3 and Technical

		resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	appendix, section 2.2
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 6, paragraph 3
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 5, paragraph 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 6-7 (Assumptions) and Technical appendix, section 1
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 7-8 (analytical methods) and Technical appendix, section 3-5
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Technical appendix, Table A1 and Section 2
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 9, paragraph 1 and Table 2.
Characterising uncertainty	20a	*Single study-based economic evaluation:*Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 9, paragraph 1 and 2, Figure 1 and Figure A7
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			

Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 11-13
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 15
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 15

Appendix 2 - Technical Appendix

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1 Description of model structures and states

The states included in each model capture the possible consequences for a patient with a PIP and the typical resource use and increased risks following an event are described. The same model structures were used for both the PIP and non-PIP scenarios with the only differences being transition probabilities and cost of the PIP or non-PIP treatment.

1.1 NSAID model

All patients start in the 'Well (no previous event)' state and remain here until they have a GI event (dyspepsia or GI bleed), an MI, or die (top, **Error! Reference source not found.**). Patients are on iclofenac 75mg twice daily in the PIP arm or paracetamol 1,000mg four times daily in the non-PIP arm. In the non-PIP arm, the transition probabilities reflect the rates of the adverse events in the general NSAID non-user population, and in the PIP arm, the relative risk in NSAID users was applied to these probabilities.

Patients can transition to the 'Dyspepsia' state where individuals have persistent dyspepsia causing GI discomfort requiring consultation with a doctor and so they attend their GP for an extra visit, are switched from diclofenac to paracetamol and receive a prescription for a proton pump inhibitor (lansoprazole 15mg once daily for four weeks). They return to the baseline (non-PIP) risk of further dyspepsia and if no further event occurs in the following cycle, they transition to the 'Well, GI event history' state.

Patients who transition to the 'GI bleed' state in this state attend the emergency department (ED), are admitted to hospital for investigation and management of upper GI bleeding, are switched from diclofenac to paracetamol and receive a prescription for lansoprazole 15mg once daily for four weeks. After discharge, they are expected to have additional healthcare use as a result of their GI bleed, namely two GP visits and two outpatient department (OPD) visits.[1,2] As with dyspepsia, they return to baseline risk of a further GI bleed and transition to the 'Well, GI event history' state if they have no further event in the following cycle. In the 'Well, GI event history' state, patients' therapy has been switched from diclofenac to paracetamol, so the cost of medication (paracetamol) and transition probabilities for further GI events or an MI from this state is equal in both the PIP and non-PIP arms.

Patients transition to the 'MI' state following an MI and remain here for one cycle unless they have a further MI in the following cycle. Patients who have an MI incur inpatient treatment costs, are switched from diclofenac to paracetamol and commence medications for secondary cardiovascular prevention. They also have an additional 11 OPD visits and attend their GP an extra 8 times in the

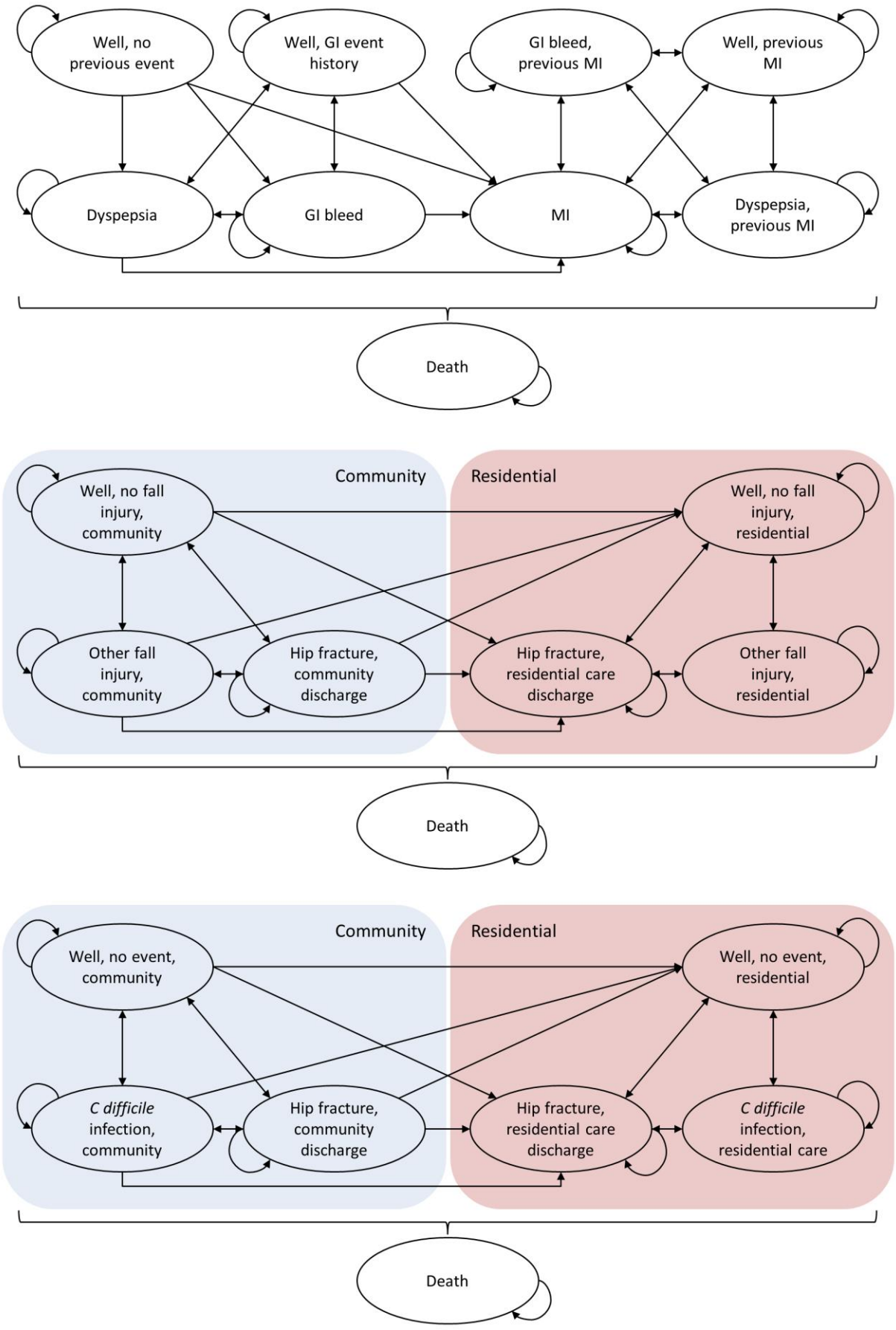

Figure A 1 Structures for NSAID (top), benzodiazepine (middle), and PPI (bottom) Markov models

year of an MI.[3] During this year patients are also at increased risk of a further MI.[4] If no event occurs in the subsequent cycle then patients transition to the 'Well, previous MI' state, where the probability of a subsequent MI falls, although it remains higher than in patients with no previous MI.[4] Patients in any 'previous MI' state incur the costs of attending two extra OPD appointments and two GP appointments per year,[3] as well as the cost of secondary preventive medicines and paracetamol.

1.2 Benzodiazepine model

All patients start in the 'Well, no fall injury, community' state as the cohort is community-dwelling and are assumed to have had no fall injury in the previous 12 months (middle, **Error! Reference ource not found.**). The only cost incurred by patients in this state is the cost of the PIP medication, diazepam 5mg twice daily in the PIP arm, whereas no pharmacotherapy is prescribed in the non-PIP arm. Patients in the PIP arm remain on this medication with its associated cost and increased adverse events risk throughout the model i.e. no therapy switch occurs after an adverse event. From this state, a transition can occur following a hip fracture or some other fall injury that a patient seeks healthcare for. Hip fractures were divided into (i) those where the patient returns home and (ii) those which result in the patient being permanently admitted to a nursing home setting. Other events that can occur independently of falls are death and admission to a nursing home.

On having a hip fracture, patients transition to one of the two hip fracture states, depending on where they are discharged to following this event and remain here for one cycle, unless they suffer a further hip fracture. All hip fracture patients present at an ED, are admitted as inpatients and are discharged either back to the community or to a residential care setting. After discharge, hip fracture patients attend an average of 9 additional OPD appointments and have an excess of 10 visits to their GP.[5] For those discharged to the residential setting, there is the additional cost of nursing home residence. For 12 months following a hip fracture patients are at an increased risk of a further fall due to their recent injurious fall.[6] If they have no hip fracture or other fall injury in the following cycle, they transition back to the 'Well, no fall injury' state (either community or residential) and return to baseline fall risk.

All patients with a fall injury requiring healthcare that is not a hip fracture (such as bruising, soft tissue injuries or other types of fractures) transition to the 'Other fall injury' state. The costs incurred in this state are based on a weighted average of the prevalence of different injury types and typical healthcare use taken from an Irish costing study.[7] Half of patients with other falls

injuries have one additional visit to their GP, 22% attend an ED, are not admitted and are referred to their GP for a follow-up visit. Twenty percent attend ED with a non-hip fracture, are admitted as inpatients, and are discharged to community where they have 9 additional OPD visits and 6 extra GP visits.[5] The remaining 8% attend ED with other fall injuries, are admitted as inpatients and following discharge, are referred for one OPD visit and one GP visit for follow-up.[8] The only difference between community and nursing home setting is the additional cost of nursing home residence. As with the hip fracture states, patients remain in this state for one cycle unless they suffer another fall injury and are at an increased risk of a further fall while in this state.

Patients from all of the community-based states transition to the 'Well, no fall injury, residential' state based on the annual probability of being admitted to a nursing home. This background probability of nursing home admission is included as otherwise the number of admissions attributed to hip fracture in benzodiazepine users would be overestimated. Patients also transition to this state in the cycle following a hip fracture which results in permanent nursing home admission, or if they are nursing home residents who suffer a hip fracture or other fall injury. As only permanent admissions are represented in this model, no transitions occur from residential states back to community states.

1.3 PPI model

The model structure (bottom, **Error! Reference source not found.**) is similar to the benzodiazepine odel. All individuals start in the 'Well, no event, community' where the only resource use is cost of the PIP or non-PIP medication (i.e. maximal dose PPI or maintenance dose PPI). Patients in each arm remain on these medications, with their associated costs and increased adverse events risk, throughout the model i.e. no therapy switch occurs after an adverse event. A number of events can then occur, those that are affected by PIP exposure (*Clostridium difficile* infection and hip fracture) and those that are unaffected (death and admission to a nursing home). Similarly, following a transition to a residential state, patients remain there and no transition back to community can occur.

Following a hip fracture, patients transition to one of the 'Hip fracture' states (again depending on the setting they are discharged to) and remain in this event state for one cycle, unless they suffer a further hip fracture. Regarding healthcare utilisation, the same pattern that applied to this state in the benzodiazepine model was used here, including the additional cost of nursing home care for residential states.

Patients who develop *C. difficile infection* transition to the '*C difficile* infection' state for one cycle where the healthcare resource use is the cost of inpatient management attributable to the infection, as community-dwelling patients aged 65 years or over are likely to be admitted as a result of an infection.[9] No further healthcare costs are incurred, and there is no increased risk of recurrence following a case (as recurrent cases were included in the baseline probability used) or being in a residential setting.

2 Sources of model inputs

The parameter inputs used in each model, along with the sources for these and the distributions used in the probabilistic sensitivity analysis are provided in Table A 1. The sources of each input are described in more detail below.

2.1 Transition probabilities

2.1.1 NSAID model

The probability of dyspepsia for non-NSAID users and the relative risk associated with NSAID use were taken from a meta-regression of trials and large exposure observational studies.[10,11] In these studies, a hypothesis was stated a priori that the prevalence in trial placebo groups would be lower than in the general population due to a selection bias in trials enrolling healthier patients. Therefore the probability was obtained by applying the relative risk to the prevalence from included NSAID versus NSAID trials. For GI bleeds, a pooled incidence rate in people aged 65 years and over from a review of epidemiological studies was used to calculate the probability.[12] Higher estimates have been reported, however these sources included NSAID users in the study populations. The risk of GI bleeds associated with naproxen and other NSAIDs was taken from a meta-analysis of randomised controlled trials.[13] The same risk of death following a GI bleed was applied to NSAID users and non-users,[14] and a UK hospital based study was the source of age-specific excess mortality estimates.[15] The baseline probability of an MI was estimated from an observational study of NSAID non-users aged 65 years and over and applied to all states with no previous MI,[16] and the probability of a further MI in the 12 months after an event was taken from a recent English population-based study.[4] This study was also the source for the probability of a subsequent MI more than one year post-MI which was applied to the previous MI states.[4] The pooled relative risk of MI on NSAIDs in the PIP arm was taken from the same meta-analysis of trials which yielded the effect on GI bleeds.[13] Probability of death in the year following an MI was taken from a study which provided the cumulative in-hospital and post-discharge mortality rate in a French cohort.[17] The long-term increase in relative mortality post MI was taken from a population-based study and applied to background mortality rate.[4] As this incorporated deaths from further MIs, the mortality from re-infarction was subtracted from this.

The increased risk of dyspepsia, GI bleeds, and MI in the PIP arm only applied to patients in the Well, no previous event state as any transition from this state following an event resulted in a switch from an NSAID to paracetamol. This switch from PIP to the non-PIP option after an adverse event was only applied to the NSAID model, not the benzodiazepine or PPI models. In the former

case patients/doctors may be reluctant to stop the benzodiazepine or it may be felt that stopping would pose a greater risk than continuing in older patients,[18] and for the latter a causal link between PPI exposure and adverse events is unlikely to be made.[19] The impact of relaxing this structural assumption for the NSAID model was assessed in sensitivity analysis.

2.1.2 Benzodiazepine model

This model only concerns falls which result in costs to the health service, therefore falls which result in no injury or falls injury which people do not seek healthcare for were excluded. The probability of a hip fracture was taken from a study reporting number of cases by age group from Irish hospital inpatient data.[7] This source was used in preference to another based on Irish data which provided similar estimates but which were presented separately by sex.[20] The estimate of the proportion of patients who are permanently admitted to a nursing home following hip fracture was taken from a cohort study in Northern Ireland which followed up patients one year post-fracture.[21] For the probability of other fall injuries, the probability of hip fracture was subtracted from the age-specific probability of an injurious fall.[22–25] The same probabilities for hip fracture and other fall injuries were applied to community and residential states. As no trials or meta-analysis of trials have been powered to detect the effect of benzodiazepines on falls, the estimate from the most recent meta-analysis of observational studies was used,[26] and two further meta-analyses had similar results.[27,28] An increased risk of a fracture or other fall injury was applied in the 12 months following a fracture or fall and this effect was taken from a meta-analysis of observational studies which reported the relative risk of a fracture in the year following a fracture.[6] The only attributable mortality included in this model was due to hip fracture,[29,30] and the relative hazard of mortality one year post fracture from a meta-analysis was applied to the all-cause mortality rate.[31] Background age-specific probability of nursing home admission (independent of hip fracture) was calculated from Irish data on the prevalence of nursing home residence.[32]

2.1.3 Proton pump inhibitors model

The probability of hip fracture, the joint probability of being admitted to a nursing home in the 12 months following a hip fracture, the relative mortality hazard in the 12 months following hip fracture, and the probability of admittance to a nursing home independent of hip fracture were taken from the same sources as the benzodiazepine model. The probability of *C. difficile* infection was based on the Irish national clinical guidance which reports the incidence in 2013.[9] The adjusted hazard ratio for mortality following *C. difficile* infection was taken from a propensity score matched-pairs analysis.[33] The source used for the increased risk of hip fracture in the PIP arm

relative to the non-PIP arm was a systematic review and meta-analysis of observational studies,[34] while the dose effects of PPIs on *C. difficile* infection was taken from a single observational study which reported this.[35] The inputs used were the risks in maximal dose PPI users relative to non-users divided by the risks in maintenance dose users relative to PPI non-users. For both fractures and *C. difficile*, there was no evidence of a significant difference between maximal dose and maintenance dose PPI users as reflected by overlapping confidence intervals, and in the case of hip fracture, the Cochran Q test for non-combinability. While this could not be accounted for in the point estimate, this was incorporated into the probabilistic sensitivity analysis when distributions were specified for these estimates.

2.2 Costs

The inpatient cost for managing a GI bleed was taken from the HSE National Casemix Programme Ready Reckoner report which provides the average cost per case for various DRGs for 39 national hospitals participating in the National Casemix Programme.[36] This was consistent with the findings of an Irish study of patients admitted from a hospital ED with low-risk non variceal GI bleeding.[37] A study conducted in a large Irish hospital used a micro-costing approach was the source for the inpatient costs of a myocardial infarction.[38] Inpatient costs for hip fracture were taken from a previous economic evaluation which reported Irish cost data,[20] while for other fall injuries, the cost input was an average of the resource use weighted by the prevalence of different types of injuries, using Irish hospital costs for inpatient stays.[7] No Irish inpatient data was available on costs of *C. difficile* infection however a European systematic review provided several estimates, of which costs from a Northern Irish study were used and the impact of using other estimates from this review were examined in sensitivity analysis.[39,40]

For other healthcare utilisation, the typical excess number of OPD and GP visits post-discharge were taken from published case-control studies for GI bleeds,[1,2] MI (both in the first and in subsequent years post-event), [3] hip and other fractures,[5] and other non-fracture fall injuries.[8] The average cost of an OPD visit was taken from the HSE National Casemix Programme,[36] and cost per GP visit was calculated based on the average annual payment by the health service to GPs per GMS patient and the mean number of visits per patient.[41,42] The cost of attending an ED used was the average reported by the National Casemix Programme.[36] Medication costs were calculated using 2014 data from the HSE-PCRS for ingredient costs and a pharmacist dispensing fee of €5 was added for each month's supply to reflect the cost to the health service. As each PIP indicator refers to a drug class, the medication most frequently prescribed in cases of PIP in a recent Irish population

study was used i.e. diclofenac, diazepam and lansoprazole for NSAIDs, benzodiazepines and PPIs respectively.[43] The cost of one year's supply of one DDD per day was used. The costs of these PIP and non-PIP medications were varied in one-way sensitivity analyses over the range of costs of different drug molecules. In probabilistic sensitivity analysis, higher variance was included in the distributions for PPI costs as these are subject to continued price reductions through reference pricing.[44] The cost of secondary preventive medications (aspirin 75mg, atenolol 50mg, ramipril 5mg, and simvastatin 20mg) was included for the MI and post-MI states. The annual cost to the health service for a person in nursing home residence was determined from 2014 data on HSE spending on the Nursing Home Support Scheme and the number of individuals funded through this.[45]

2.3 Utilities

The preferences used in weighting for QALYs can be directly measured using rating scale, standard gamble or time trade off (TTO) methods. Ratings scales such as the EQ-5D visual analogue scale (VAS) ask participant's to rate a health state (either their own or one described to them) on a visual analogue scale ranging from 0 to 1. Although straightforward to administer, ratings scales can lead to end-aversion bias, where participants avoid values close to 0 or 1, and as there is no choice involved or 'cost' to stating a very weak or strong preference, people tend to overstate their preferences. The standard gamble method generally presents participants with two alternative scenarios, either certainty of being in a health state e.g. for a chronic disease, or a gamble between full health and some probability of death. This probability is varied until the participant is indifferent between the two options and the probability is the utility of the health state. This method is often held as the gold standard but can be challenging to employ due to difficulty people may have interpreting probabilities and because its complexity usually requires delivery in an interview. A simpler alternative is the time trade off method. It presents individuals with the option of spending a set time in the health state of interest or a shorter amount of time in full health, the time in full health is varied until there is indifference between the options and the utility is calculated by dividing the time in full health by the time in the health state of interest. This approach is simpler than the standard gamble which may make it more versatile as it may not need to be administered face-to-face.

As these methods can be time-consuming and complex to use, an alternative is multi-attribute utility systems such as the EQ-5D. Firstly, patients describe the health state they are in using a generic descriptive system of attributes which captures all important dimensions of the state.

Secondly, valuations for each of these attributes derived from the general public are combined to determine an overall quality for the health state. In the EQ-5D, five attributes are included (Mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and for each of these three response levels are defined. For example, under mobility people can select "I have no problems in walking about", "I have some problems walking about" and "I am confined to bed". A valuation or tariff is estimated for all possible health states (3^5 = 243) by a large sample of individuals valuing each state using the TTO method. Coefficients are derived for each level of each attribute using regression, which are combined as a decrement from a utility of 1.0 to give a utility for each state.

2.3.1 NSAID model

Disutilities for dyspepsia and GI bleeds were based on directly elicited utilities,[46,47] and the typical period of time patients would suffer symptoms for.[48] This is consistent with previous economic modelling methods,[49] and the disutility was calculated as follows:

$$(1 - utility\ of\ health\ state) \times \frac{Time\ in\ health\ state\ in\ days}{365\ days}$$

The disutility in the year following an MI was taken from a study reporting the annual utility loss associated with various cardiovascular events adjusted for patient characteristics using regression methods.[50] As evidence was conflicting regarding whether there was a long-term quality of life impact following an MI,[51,52] the most conservative estimate in the literature of MI disutility in subsequent years was applied, and a wide distribution was used in probabilistic sensitivity analysis to reflect the uncertainty around this value.[53] The most robust estimates of utility loss following fractures are from two systematic reviews and one Swedish study which uses three different scenarios to analyse the disutility in the 12 months following various fracture types and were similar across these studies.[54–56] The disutility for hip fracture was taken from the systematic review which included the greatest number of studies, and the utility loss in the year following a wrist fracture from this study was applied to the other fall injury state.[56] A disutility was applied to all residential states, consistent with previous economic models relating to hip fractures, on the basis that individuals who are institutionalised are likely to have some impairment in the dimensions captured by the EQ-5D such as mobility, self-care, or usual activities.[57,58] The input used was based on the utility difference between carers of Alzheimer's disease patients in the community and in nursing home residence.[59] The annual utility loss due to *C. difficile* was based on the utility of being hospitalised and the likely duration of hospital stay, calculated using the equation above.[60,61]

2.3.2 Benzodiazepine model

The most robust estimates of utility loss following fractures are from two systematic reviews and one Swedish study which uses three different scenarios to analyse the disutility in the 12 months following various fracture types.[54–56] Estimates from these studies have been used in a number of fracture-related economic evaluations and were similar across the three studies, with utility loss in the year following hip fracture in the range of 0.17 to 0.30 and for wrist or forearm fractures in the range of 0.044 to 0.1. The disutility for hip fracture used in this model was 0.203 (95% CI 0.175, 0.23) taken from Hiligsman and colleagues. as this was based on more studies than the review by Peasgood and colleagues.[56] For other fall injuries, the disutility associated with a wrist fracture from Hiligsman and colleagues. of 0.06 (95% CI 0.04, 0.09) was applied to this state. No disutility was applied directly to the subsequent years following a hip fracture or other fall injury in the interests of model simplicity, so this may underestimate the QALY loss following such an event. However a disutility was applied to all residential states on the basis that individuals who are institutionalised are more likely to have some impairment in the dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (which are included in the EQ-5D). The value used was 0.06 (95% CI 0.03-0.338) which had previously been applied in two economic models relating to hip fractures.[57,58] The original source was a study of Alzheimer's disease, using carers as proxy respondents.[59] The disutility was derived from the difference in preference weight between carers of patients in community and those in nursing home residence and this difference was constant in both moderate and severe Alzheimer's disease.

2.3.3 PPI model

The disutility of hip fracture and residence in a nursing home were the same as those used in the benzodiazepine model. The disutility of a case of *C. difficile* does not seem to have been directly elicited in any study using the EQ-5D or TTO methods. Several economic evaluations relating to *C. difficile* cases have included a range of utility decrements, based on the utility of being hospitalised and the likely duration of hospital stay,[60,61] or the disutility of diarrhoea symptoms.[62] The former method was used as it was similar to that adopted for the disutility of a GI bleed in the NSAID model. Applying a 14 day attributable length of stay (which was taken from a UK study and is approximately the median value in a review of excess LOS),[63] the disutility input used in this model was 0.026.[60,61]

Table A 1 Point estimates for each parameter input and distributions used in probabilistic sensitivity analysis

Parameter description	Value	Distribution	Source
NSAID model			
Transition probabilities			
Probability of dyspepsia in non-NSAID users	0.0497	Beta (4,058, 75,513)	[10,11]
Probability of GI bleed in non-NSAID users	0.0013	Beta (99.71, 76,601.91)	[12,13]
Probability of death following GI bleed by age group		Beta	[64]
60-79	0.11	(156, 1,265)	
80+	0.2	(174, 698)	
Probability of an MI in non-NSAID users	0.0082	Beta (419, 50775)	[16]
Probability of an MI in the 12 months following an MI	0.064	Beta (2339.94, 34221.56)	[4]
Probability of an MI in subsequent years after an MI	0.0143	Beta (1378.65, 95030.28)	[4]
Probability of death following an MI	0.097	Beta (209, 1942)	[17]
Probability of death by age group			
65-69	0.0121		[65]
70-74	0.0198		
75-79	0.0340		
80-84	0.0644		
85+	0.1495		
Effect			
Relative risk of dyspepsia in long-term NSAID users	1.4	Log-normal (0.336, 0.126)	[10,11]
Relative risk of GI bleed in long-term NSAID users	3.07	Log-normal (1.122, 0.114)	[13]
Relative risk of MI in long-term NSAID users	1.53	Log-normal (0.425, 0.174)	[13]
Relative risk of death in people >1 year post-MI	2	Log-normal (0.693, 0.088)	[4]
Utility			
Utility of being in well state		Beta	
65-74	0.77	(129.13, 38.57)	[66]
75+	0.74	(108.51, 38.13)	
Utility decrement in 12m following dyspepsia	0.0325	Gamma (129.13, 38.57)	[46,47,49]
Utility decrement in 12m following GI bleed	0.0433	Gamma (108.51, 38.13)	[46,47,49]
Utility decrement in 12m following MI	0.055	Gamma (74.37, 1352.24)	[50,51]
Annual utility decrement >12m post-MI	0.012	Gamma (4, 333.33)	[51–53]
Costs			
Cost of NSAID treatment	149.64	Gamma (100, 0.668)	[67]
Cost of paracetamol treatment	97.68	Gamma (100, 1.024)	[67]
Cost of managing dyspepsia	152.64	Gamma (100, 0.655)	[67]
Cost of managing a GI bleed	4,983.68	Gamma (44.44, 0.009)	[36,37,67]
Cost of managing an MI	9,856.67	Gamma (100, 0.010)	[3,36,38]
Cost of a previous MI	819.56	Gamma (100, 0.122)	[3,67]
Benzodiazepine model			
Transition probabilities			
Probability of an injurious fall requiring healthcare utilisation			[22–25]
		Beta	
65-79	0.0476	(95, 1,905)	
80+	0.1	(200, 1,800)	
Probability of a hip fracture		Beta	[12,13]
65-69	0.0014	(197, 140,517)	
70-74	0.0031	(357, 114,804)	
75-79	0.0066	(597, 89,858)	

Parameter description	Value	Distribution	Source
80-84	0.0152	(961, 62,263)	
85+	0.0247	(1,071, 42,289)	
Probability of being in nursing home at 12m following a hip fracture	0.11	Beta (224, 1,810)	[64]
Probability of being admitted to nursing home in general population			[32]
		Beta	
65-69	0.0021	(301, 143,095)	
70-74	0.0033	(393, 118,759)	
75-79	0.0065	(601, 91,865)	
80-84	0.0151	(980, 63,904)	
85+	0.0241	(1,093, 44,254)	
Effect			
Relative risk of an injurious fall in long-term benzodiazepine users	1.553	Log-normal (0.440, 0.043)	[26]
Relative risk of injurious fall in 12 months post-fall injury	2.0	Log-normal (0.693, 0.039)	[6]
Relative hazard of death in 12 months following a hip fracture relative to people without fracture	3.26	Log-normal (1.182, 0.062)	[31]
Utility			
Utility decrement in 12m following a hip fracture	0.203	Gamma (209.33, 1,031.2)	[55,56]
Utility decrement in 12m following other fall injury	0.06	Gamma (22.13, 368.79)	[55,56]
Utility decrement of being resident in nursing home	0.06	Gamma (0.58, 9.72)	[57–59]
Costs			
Cost of benzodiazepine treatment	77.92	Gamma (100, 1.283)	[67]
Cost of hip fracture	17,394.47	Gamma (385.34, 0.022)	[5,20,67]
Cost of other fall injury	2,782.39	Gamma (25, 0.009)	[5,7,8,67]
Cost of residence in nursing home	42,670.00	Gamma (9,407.98, 0.220)	[45]
PPI model			
Transition probabilities			
Probability of having *C. difficile* infection	0.00358	Beta (1839, 511,848)	[9]
Effect			
Relative risk of hip fracture in maximal dose PPI users relative to non-users	1.462	Log-normal (0.380, 0.097)	[34]
and maintenance dose PPI users relative to non-users	1.247	Log-normal (0.221, 0.050)	
Relative risk of *C. difficile* infection in maximal dose PPI users relative to non-users	2.349	Log-normal (0.854, 0.140)	[35]
and in maintenance dose PPI users relative to non-users	1.735	Log-normal (0.551, 0.114)	
Relative hazard for death in 12m post *C. difficile*	1.23	Log-normal (0.207, 0.089)	[33]
Utility			
Utility decrement in 12m post *C. difficile*	0.026	Gamma (0.530, 20.38)	[60,61,63]
Costs			
Cost of max dose PPI treatment	160.80	Gamma (25, 0.155)	[67]
Cost of maintenance dose PPI	117.12	Gamma (25, 0.213)	[67]
Cost of *C. difficile*	5,837.32	Gamma (19.3, 0.003)	[9,39,40]

3 Probabilistic sensitivity analysis methods

Uncertainty associated with imprecision of the parameter inputs was incorporated into the model using probabilistic sensitivity analysis (PSA) to allow 95% credible intervals (CIs) to be fitted. A distribution of possible values for each parameter was specified, which were fitted under the assumption of a homogenous sample of patients informing parameter estimates (i.e. heterogeneity between patient sub-groups was not investigated). The distribution type used for each parameter reflected the form of data the parameter takes and the standard distributional assumptions used when estimating CIs (as detailed below).[38] The distributions fitted for each parameter were calculated from data available in published sources and these are reported in Table A 1. Each model was run over 10,000 iterations and a random value for each parameter input was sampled from the specified distribution for each run. The outputs of each iteration were recorded to provide a distribution of cost and effect differences and the 2.5th and 97.5th percentiles for these differences were used to estimate 95% CIs. Statistical significance was assumed if the 95% CI for the incremental costs and effects did not include zero. The outputs of each iteration were also plotted on a cost-effectiveness (CE) plane to compare the distribution of ICER estimates for each PIP.

3.1 Approaches used to specify distributions for parameters

3.1.1 Probability parameters

As probabilities can only range between zero and one, the distribution specified must adhere to this limit so that impossible values are not selected from the distribution. A beta distribution is suitable for binomial data as it is constrained between zero and one. It is characterised by two parameters, α and β. In a single study where the number of events and sample size are known, the value of α can be set to the number of events and β to the sample size minus the number of events to specify the beta distribution for uncertainty around the probability point estimate. In the absence of this information, for example if using findings from a meta-analysis, the distribution can be fitted by the method of moments if the mean or proportion and standard error or variance are given, using the following equations:

$$\alpha = \bar{\mu}\left(\frac{\bar{\mu}(1-\bar{\mu})}{s^2} - 1\right)$$

$$\beta = \alpha.\frac{(1-\bar{\mu})}{\bar{\mu}}$$

3.1.2 Relative risk parameters

Relative risks (RR) are composed of ratios of ratios ranging from zero to infinity and the confidence intervals for which are calculated on the log scale. Therefore, the appropriate distribution for these parameter is lognormal and a distribution can be specified as N(ln[RR], se[ln(RR)], by taking the natural log of the point estimate and calculating the standard error of this using reported Cis as follows:

$$se[\ln(RR)] = \frac{\ln(Upper\ CI) - \ln(Lower\ CI)}{2 \text{ x } 1.96}$$

3.1.3 Cost parameters

Cost data is constrained to positive values so is generally truncated (to exclude negative values) and right-hand (or positively) skewed as there tends to be small numbers of cases with high costs on the right side of the distribution. Often Poisson or gamma distributions are used to represent cost data, although lognormal distributions can also be used. A gamma distribution can be fitted with the method of moments. For gamma(α,β), the mean ($\bar{\mu}$) is equal to αβ and the variance (s^2) is equal to $\alpha\beta^2$, which can be rearranged to

$$\alpha = \frac{\bar{\mu}^2}{s^2}$$

$$\beta = \frac{s^2}{\bar{\mu}}$$

3.1.4 Utility parameters

Utility parameters tend to fall within the range zero to one, however they can technically range into negative values, representing states worse than the reference 'worst health state' used to derive them (usually death). For utilities far from zero, a beta distribution can be used. Another approach is to use the disutility or utility decrement for a health state (1 – utility), which are constrained between zero and positive infinity and can be specified as gamma or lognormal distributions.

4 TreeAge Pro model structures

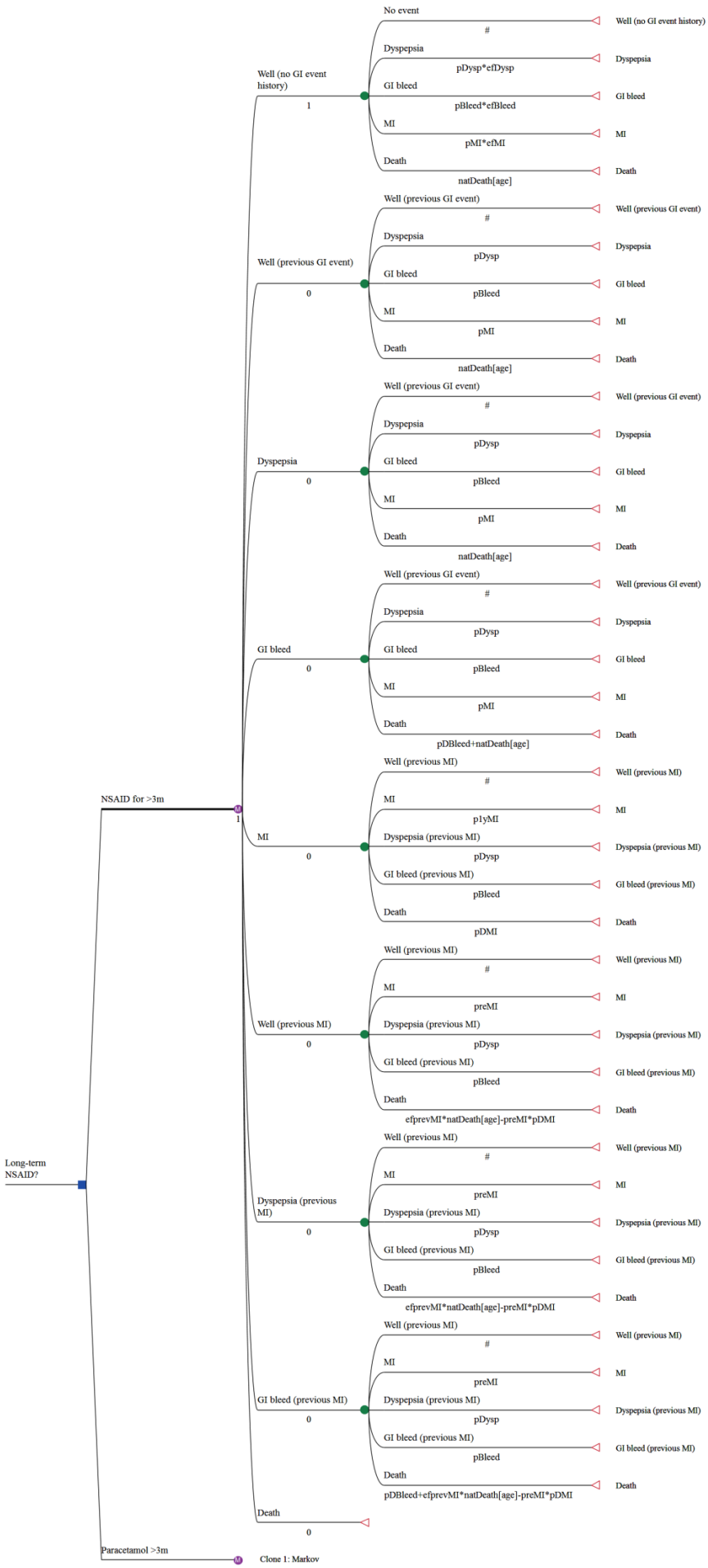

Figure A 2 Decision tree structure for NSAID Markov model in TreeAge Pro

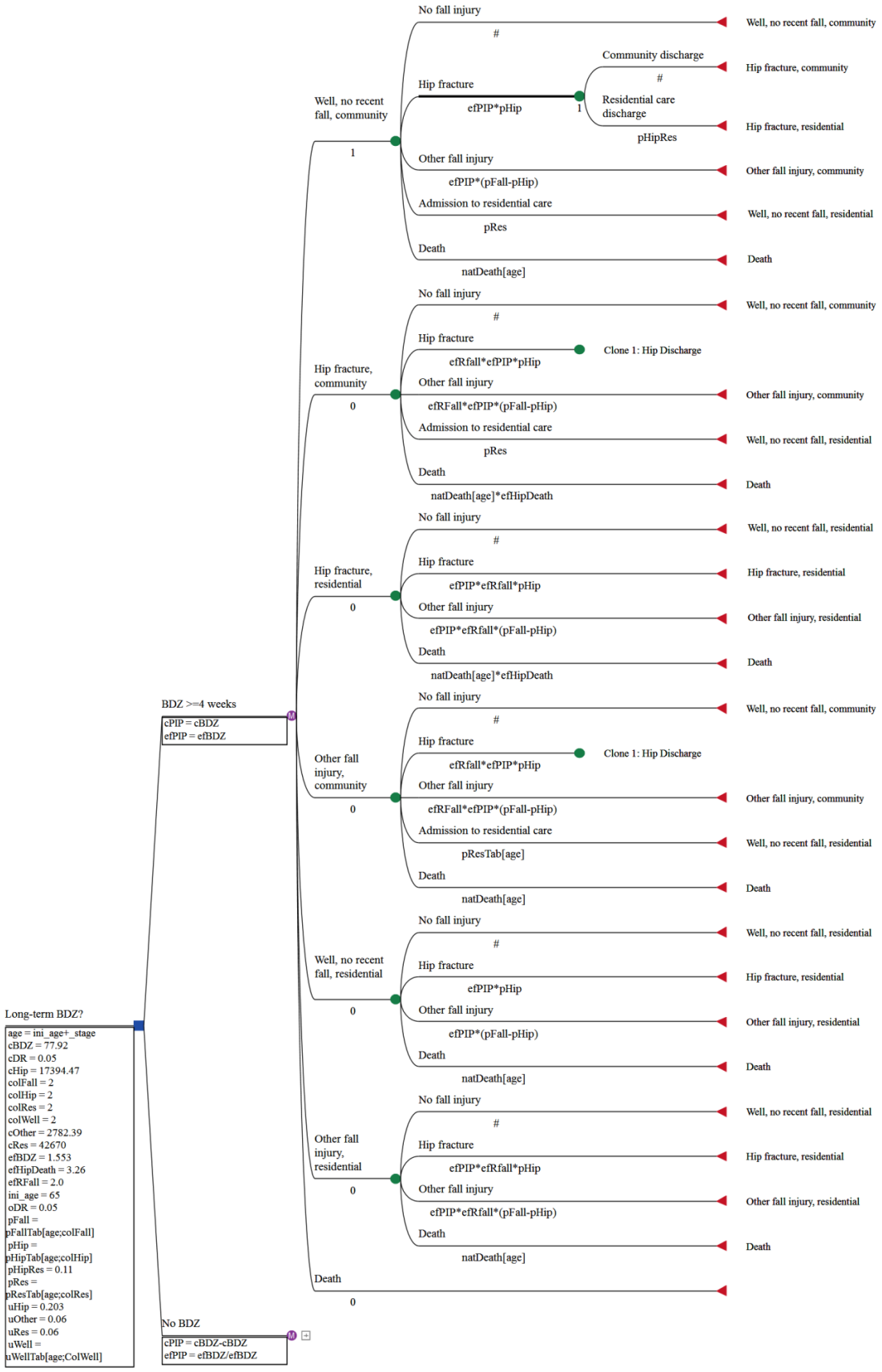

Figure A 3 Decision tree structure for benzodiazepine Markov model in TreeAge Pro

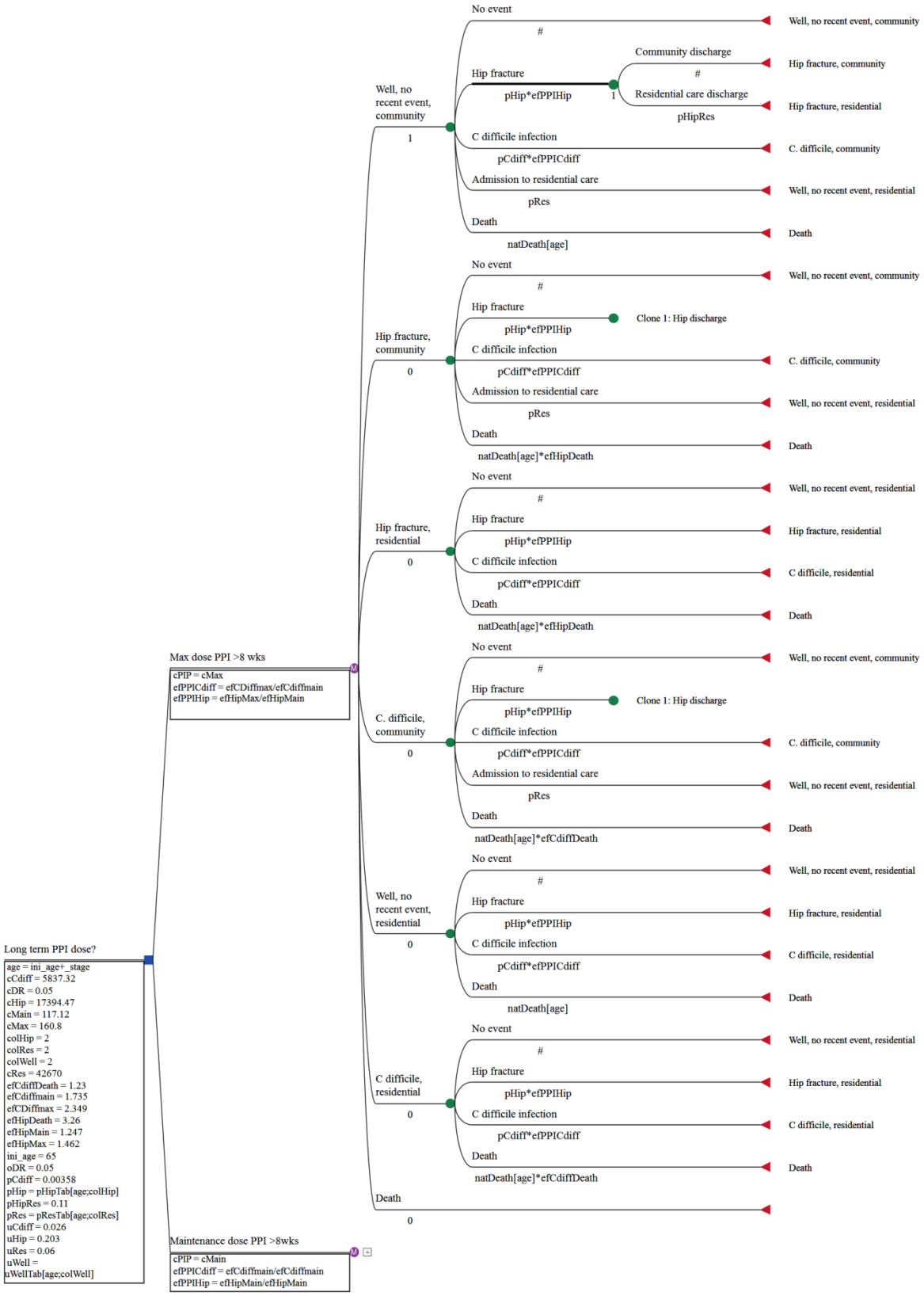

Figure A 4 Decision tree structure for PPI Markov model in TreeAge Pro

5 Published estimates of intervention effectiveness

In the OPTI-SCRIPT trial of a complex intervention in general practice, the relative risk of being on a long-term maximal dose PPI post-intervention was 0.45 (i.e. a 55% reduction) compared to usual care.[68] For NSAIDs, a recent trial of education, informatics and incentives in general practice demonstrated a significant reduction of 49.8% in high-risk prescribing relating to NSAIDs and gastroprotection (i.e. a risk reduction of 0.498).[69] A trial to reduce inappropriate prescribing of benzodiazepines using direct patient education demonstrated an additional 23% of those in the intervention group had discontinued benzodiazepines compared to control (i.e. a risk reduction of 0.23).[70]

In the economic evaluation of potential interventions to reduce PIP, a new decision was framed between implementing an intervention to reduce PIP or usual care, as illustrated in Figure A 5 below for NSAIDs. The effectiveness estimate of the published interventions for each type of PIP was used as an input in each analysis as the proportion of patients receiving the intervention who are switched from the PIP drug to the more appropriate alternative.

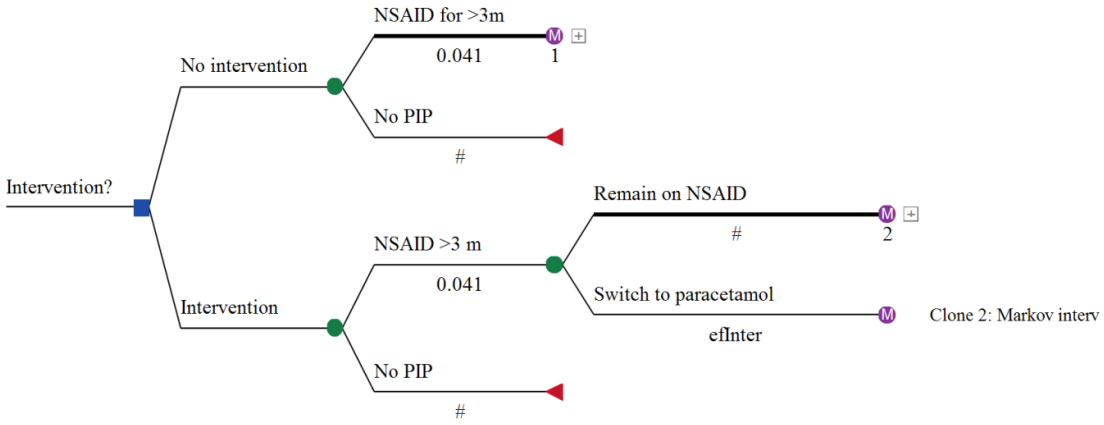

Figure A 5 Decision tree structure of published intervention analysis for NSAIDs

6 Further results of economic evaluation analysis

6.1 Base case analysis

Table A 2 provides the total cost, QALY and LY outputs of each scenario, as well as the difference in these in the PIP scenario relative to the appropriate scenario and ICERs for each model. Table A 3 reports the number of cases of adverse events in the PIP and appropriate alternative scenarios.

Table A 2 Full cost, effect, and ICER results for each model for PIP scenarios relative to non-PIP scenarios

Strategy	Cost (€)	Incr. Cost (€)	QALYs	Incr. QALYs	ICER (€ per QALY)	LYs	Incr. LYs
NSAID model							
Paracetamol >3m	2,602.52		8.72			11.54	
NSAID for >3m	3,408.56	806.03	8.65	-0.07	-11,511.44	11.46	-0.08
Benzodiazepine model							
No benzodiazepine	25,158.00		8.78			11.69	
Benzodiazepine ≥4 wks	28,628.04	3,470.04	8.72	-0.07	-52,671.50	11.65	-0.04
PPI model							
Maintenance dose >8wks	24,830.71		8.82			11.70	
Maximal dose >8 wks	25,819.27	988.56	8.81	-0.01	-85,278.60	11.68	-0.02

Abbreviations: ICER, incremental cost effectiveness ratio; Incr., incremental; LYs, life years; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; QALYs, quality-adjusted life years.

Table A 3 Number of adverse events for PIP and non-PIP scenarios

Adverse events	PIP cases	Non-PIP cases	Difference	NNH
NSAID model				
GI bleeds	48	25	23	43
Dyspepsia	1141	973	168	6
MIs	213	172	41	25
Benzodiazepine model				
Hip fractures	296	184	113	9
Other injuries	1864	1159	704	1.4
PPI model				
Hip fractures	195	167	28	36
C. difficile infections	94	70	24	41
Adverse events	PIP cases per 1000 person years	Non-PIP cases per 1000 person years	Difference	NNH
NSAID model				
GI bleeds	60.34	50.91	9.44	106
Dyspepsia	2.54	1.30	1.24	804
MIs	11.24	9.00	2.24	447
Benzodiazepine model				
Hip fractures	15.22	9.44	5.78	173
Other injuries	95.74	59.56	36.18	28
PPI model				
Hip fractures	10.04	8.59	1.45	689
C. difficile infections	4.84	3.57	1.27	791

Abbreviations: NNH, number needed to harm; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; QALYs, quality-adjusted life years.

6.2 Deterministic sensitivity analysis

Table A 4 present the deterministic sensitivity analysis where inputs for which there was particular uncertain around were varied individuals to determine the impact this had on the incremental costs and QALYs for each model.

Table A 4 One way deterministic sensitivity analysis results

	NSAID model	Benzodiazepine model	PPI model
	Incremental effect (QALYs)		
Outcome discount rate			
0	-0.157	-0.175	-0.035
0.02	-0.111	-0.115	-0.022
0.04	-0.082	-0.079	-0.014
0.06	-0.061	-0.056	-0.010
	Incremental cost (€)		
Costs discount rate			
0	1,145.45	6,497.62	1,767.79
0.02	984.56	4,978.65	1,379.78
0.04	858.79	3,893.76	1,099.22
0.06	758.79	3,108.09	893.40
Inpatient cost of *C. difficile*			
€4,000.00	-	-	961.63
€6,398.72	-	-	996.79
€8,797.45	-	-	1,031.94
€11,196.17	-	-	1,067.09
PIP drug cost[a]			
Low	349.20	3,016.20	478.15
High	1,125.73	4,474.65	2,166.44
Non-PIP drug cost[b]			
Low	1,192.38	-	1,673.52
High	660.57	-	477.64

[a] PIP drug cost range (€) NSAID: 74.82-202.00, benzodiazepine: 38.96-164.16, PPI: 117.12-261.60.

[b] Non-PIP drug cost range (€) NSAID: 38.40-120.00, PPI: 56.56-160.80.

6.3 Probablistic sensitivity analysis

The outputs of each iteration of the probabilistic sensitivity analysis were plotted on a CE plane to compare the distribution of ICER estimates for each PIP. Figure A 6 plots the outputs for each iteration using the alternative NSAID scenario where individuals taking NSAIDs remain on this medication following any adverse event as opposed to the base case analysis where individuals are switched to paracetamol following an adverse event.

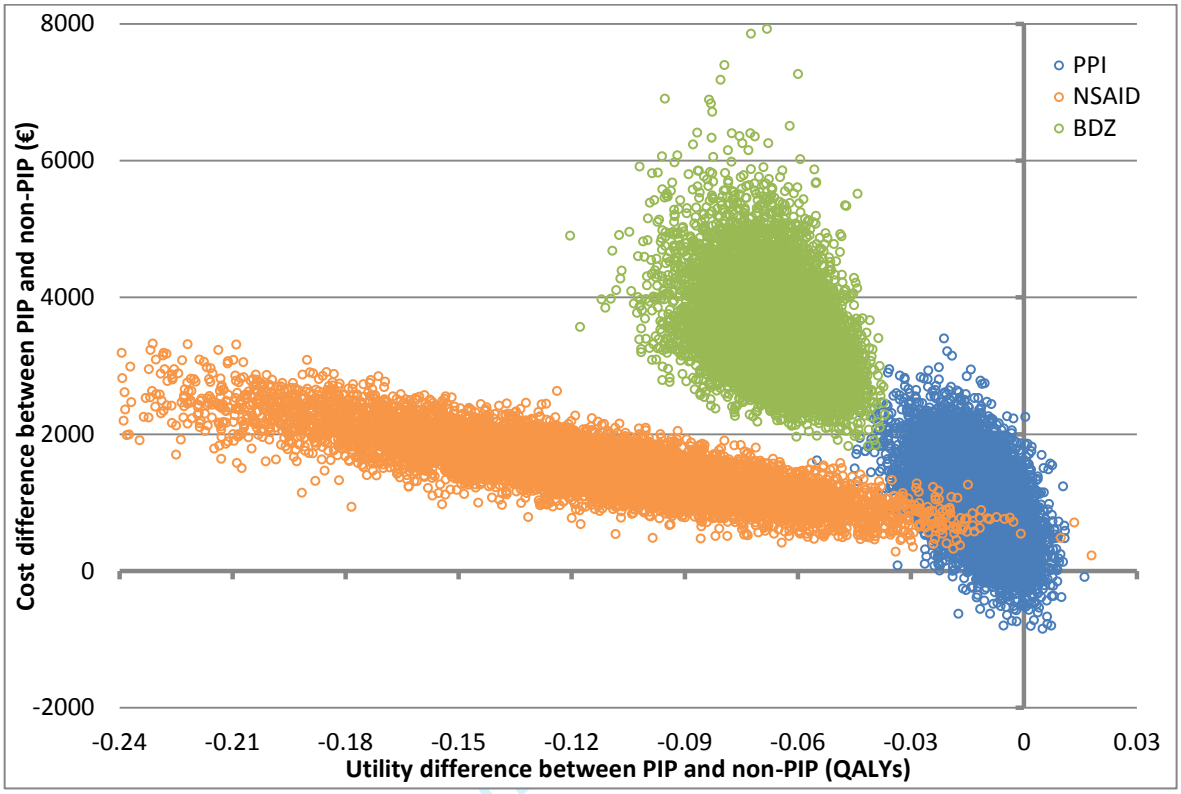

Figure A 6 Incremental costs and utilities for PIP compared to non-PIP from probabilistic sensitivity analysis using alternative NSAID scenario

6.4 Evaluation of cost-effectiveness of published interventions

The results of threshold analysis for an intervention to target NSAID prescribing are plotted in Figure A 7 showing whether the intervention is preferred to no intervention at a cost-effectiveness threshold of €45,000 per QALY as intervention cost and effectiveness vary. The arrow shows how an intercept can be used to determine the cost at which the intervention becomes cost effective given a certain effectiveness, or vice versa. For example, at a €500 intervention cost, the intervention targeting NSAID prescribing would be cost effective if it reduces PIP by at least 12.6%.

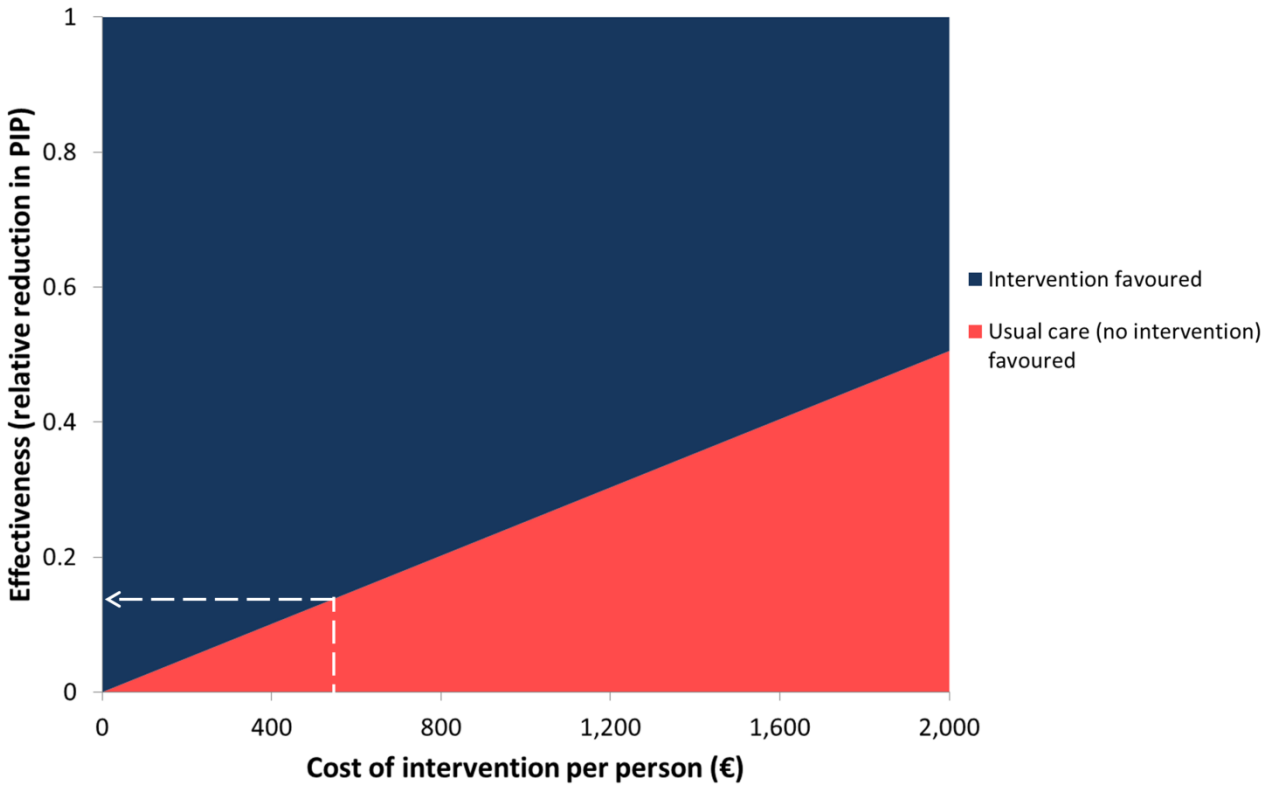

Figure A 7 Threshold effectiveness value for NSAID intervention at intervention cost of €500 and cost-effectiveness threshold of €45,000 per QALY

7 References

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Section/item	Item No	Recommendation	Reported on page No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 4, paragraph 1
		Present the study question and its relevance for health policy or practice decisions.	Page 4, paragraphs 2-3
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 5, paragraph 1
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 5, paragraph 1
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 5, paragraph 1
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 5, paragraph 1 and Table 1
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5 paragraph 1
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 5, paragraph 1
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 5, paragraph 1 and Page 6, paragraphs 2-3
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Technical appendix, section 2.1
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Page 6, paragraph 2 and Technical appendix, section 2.3
Estimating resources and costs	13a	*Single study-based economic evaluation:*Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate	Page 6, paragraph 3 and Technical

		resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	appendix, section 2.2
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 6, paragraph 3
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 5, paragraph 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 6-7 (Assumptions) and Technical appendix, section 1
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 7-8 (analytical methods) and Technical appendix, section 3-5
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Technical appendix, Table A1 and Section 2
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 9, paragraph 1 and Table 2.
Characterising uncertainty	20a	*Single study-based economic evaluation:*Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 9, paragraph 1 and 2, Figure 1 and Figure A7
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			

Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 11-13
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 15
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 15

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Economic impact of potentially inappropriate prescribing and related adverse events in older people: a cost-utility analysis using Markov models

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Economic impact of potentially inappropriate prescribing and related adverse events in older people: a cost-utility analysis using Markov models

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Abstract

Objectives: To determine the economic impact of three drugs commonly involved in potentially inappropriate prescribing (PIP) in adults aged ≥65 years, including their adverse effects (AEs): long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, and proton pump inhibitors (PPIs) at maximal dose; to assess cost-effectiveness of potential interventions to reduce PIP of each drug.

Design: Cost-utility analysis. We developed Markov models incorporating the AEs of each PIP, populated with published estimates of probabilities, health system costs (in 2014 euro), and utilities.

Participants: A hypothetical cohort of 65 year olds analysed over 35 one-year cycles with discounting at 5% per year.

Outcome measures: Incremental cost, Quality-Adjusted Life Years (QALYs) and incremental cost-effectiveness ratios with 95% credible intervals (CIs, generated in probabilistic sensitivity analysis) between each PIP and an appropriate alternative strategy. Models were then used to evaluate the cost-effectiveness of potential interventions to reduce PIP for each of the three drug classes.

Results: All three PIP drugs and their AEs are associated with greater cost and fewer QALYs compared to alternatives. The largest reduction in QALYs and incremental cost was for benzodiazepines compared to no sedative medication (€3,470, 95%CI €2,434, €5,001; -0.07 QALYs, 95%CI -0.089, -0.047), followed by NSAIDs relative to paracetamol (€806, 95%CI €415, €1,346; -0.07 QALYs, 95%CI -0.131, -0.026), and maximal dose PPIs compared to maintenance dose PPIs (€989, 95%CI -€69, €2,127; -0.01 QALYs, 95%CI -0.029, 0.003). For interventions to reduce PIP, at a willingness-to-pay of €45,000 per QALY, targeting NSAIDs would be cost-effective up to the highest intervention cost per person of €1,971. For benzodiazepine and PPI interventions, the equivalent cost was €1,480 and €831 respectively.

Conclusions: Long-term benzodiazepine and NSAID prescribing are associated with significantly increased costs and reduced QALYs. Targeting inappropriate NSAID prescribing appears to be the most cost-effective PIP intervention.

Strengths and limitations of this study

- This study represents a novel application of economic modelling methods to assess three common types of potentially inappropriate prescribing.
- Analysis included the principal adverse effects of each potentially inappropriate medication.
- Uncertainty of estimates was quantified using probabilistic sensitivity analysis.
- The study did not consider differences in adverse event risk among individual drugs within each class, or heterogeneity in economic impact among patient sub-groups.

Introduction

Potentially inappropriate prescribing (PIP), the use of medicines where the risks outweigh the benefits, is prevalent among adults aged ≥65 years, particularly in individuals taking multiple medicines or with multiple chronic conditions.[1,2] Several explicit measures of PIP have been developed, including Beers criteria and the Screening Tool for Older Person's Prescriptions (STOPP), and while their relationship with some patient outcomes has been evaluated, the effect on the wider health system is also important to consider, in particular on healthcare costs.[3] The use of potentially inappropriate medicines can have an impact on health care costs due to pharmaceutical expenditure relating to the prescriptions themselves and due to managing the adverse events which may result. In two systematic reviews, one of studies assessing the STOPP criteria and another on the economic impact of inappropriate drug prescribing more generally, only direct medication costs of PIP drugs were assessed.[3,4] Increased life expectancy has called into question the use of 65 years and above as a threshold for old age, however the literature on PIP (including STOPP) still focuses on this population due to physiological changes in ageing and the prevalence of multiple co-morbidities which can predispose to medication harm.[3]

Furthermore, in only assessing the direct cost of inappropriate drugs, the economic consequences of appropriate prescriptions used as an alternative to PIP medicines are not accounted for.[4,5] The costs of managing any resulting adverse events have yet to be quantified for PIP as a whole, and have only been assessed for individual medication classes to date, such as benzodiazepines and NSAIDs.[6–8] The economic impact of PIP is important when considering whether interventions to reduce PIP are an efficient use of resources and health professionals' time relative to other competing priorities. Few economic evaluations of trials to optimise prescribing for older people have been published,[3,9,10] which may limit implementation of such interventions by decision-makers, given scarce healthcare resources.

A recent analysis of PIP among older adults in Ireland found that the most common indicators related to long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, and maximal dose proton pump inhibitors (PPIs).[2] NSAIDs are indicated for treating pain in arthritis and low back pain for example, however due to their gastrointestinal and cardiovascular risks, they are not recommended for long-term use. Benzodiazepines are sedative agents used to treat insomnia, but carry risks of day-time drowsiness as well as tolerance and dependence following long-term use. PPIs are used for gastrointestinal conditions such as peptic ulcer disease and gastro-oesophageal reflux disease. While maximal doses are indicated for up to 8 weeks in the majority of

cases, following this a maintenance dose has comparable efficacy if continued treatment is necessary. Despite strong evidence that the balance of benefits and harms for such prescriptions is unfavourable, the prevalence of these indicators ranged from 4% to 24% in a primary care population analysis (where most prescribing of these agents occurs).[2]

The aim of this study is to estimate and compare the economic impact of these three common indicators of PIP: long-term use of NSAIDs, benzodiazepines, and maximal dose PPIs. Specifically, we compare each of the three PIP drugs to a more appropriate treatment using Markov models to assess differences in quality and quantity of life and cost to the health system. We then apply the models to explore the cost-effectiveness of potential interventions based on recently published trials targeting these PIP drugs.

Methods

Markov models

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement was used in the design and reporting of this research (included as Appendix 1).[11] A Markov model was developed for each of the included PIP drugs using TreeAge Pro 2015 (TreeAge Software Inc., Williamstown, MA). This type of decision-analytic model was chosen to allow for time dependency, a particularly important consideration in the context of older people on long-term medicines.[12] The base case analysis used a target population of hypothetical 65 year olds who were community-dwelling in Ireland and had no current or previous adverse events relating to these PIP drugs. A health system perspective was used over a time horizon of 35 one-year cycles (i.e. to age 100) with a half cycle correction.[13] This perspective is recommended in national guidelines on economic evaluation,[14] and therefore only direct costs to the health system (including those relating to residential care) were considered. The primary decision maker is therefore Ireland's Health Service Executive which makes funding allocation decisions relating to health technologies. In each of the three cases, the PIP strategy was compared to an alternative strategy, selected as an appropriate therapeutic option instead of the PIP drug (with respect to effectiveness and safety). The models incorporated the principal adverse drug events relating to each PIP (see Table 1). The primary outcomes evaluated were costs and quality-adjusted life years (QALYs). Life years (LYs) and number/rate of adverse events were also quantified as secondary outcomes. A discount rate for costs, QALYs, and LYs was applied at 5% per annum, and was varied from 0% to 6% in sensitivity analysis, in line with guideline recommendations.[14]

This cohort consisted of healthy community-dwelling older people, therefore in each model, all individuals start in a 'Well' state (see Figure A1 in Appendix 2 for state transition diagrams for each model). In subsequent cycles, individuals could transition to other states as a result of adverse events relating to the potentially inappropriate medicines of interest. Individuals remain in the adverse event state for one cycle unless they have a further adverse event in the subsequent cycle, and otherwise they transition to the post-event state (if applicable) or the relevant 'Well' state. Mortality attributable to adverse events and background age-related mortality were included. An in-depth description of the structure and transitions for each model is included in section 1 of Appendix 2. The models were populated with parameter estimates (see Table A1) derived from published sources which are described in detail in section 2 of Appendix 2.

Model inputs

Transition probabilities

Probabilities of transitions between states for the three models were taken from published literature sources which reported rates or probabilities of the adverse events of interest. Population-based epidemiological studies with study samples representative of older community-dwelling adults were used, whenever possible, reflecting the baseline rate of adverse events for individuals in the appropriate alternative models (see Table A1). In the PIP models, a measure of the relative risk associated with the PIP drug was applied to the baseline probability for each adverse event. These were taken from meta-analyses of randomised controlled trials for NSAIDs,[15–17] meta-analyses of observational studies for benzodiazepines,[18,19] and for PPIs from a meta-analysis of observational studies,[20] and a single observational study.[21]. Annual probability of death from all causes was based on age-specific population rates for 2014 from the Central Statistics Office (CSO).[22] Excess mortality estimates following adverse events were taken from observational studies,[23–28] and were assumed to be independent of PIP exposure (i.e. the same post-event mortality was applied in both PIP and alternative scenarios).

Utility values

To increase comparability between the models, the same baseline utility value was applied to all 'Well' or no event health states. The source of these values were UK population norms for the EQ-5D visual analogue scale for people aged 65-74 and 75 years and over.[29] Utility decrements or disutilities, the annual reduction in utility due to an adverse event were taken from previous economic evaluations or studies that derived these values from patients with the relevant adverse event.[9,30–43] These were subtracted from this baseline utility to give the utility value for each state. Further details of these are provided in Appendix 2, section 2.3.

Costs

Each state was assigned a cost reflecting the average annual costs to the Irish health system for a patient in that health state, relating to hospital inpatient care, general practitioner, out-patient department, and emergency department visits, medicines, and long-term (residential) care. Costs in euro from 2014 were used, and, where not available, historical costs were inflated using the applicable Consumer Price Index Health sub index from the CSO. In the case of *C. difficile* infection, international estimates of attributable costs were inflated to 2014 costs using the CPI from the origin country, and were then converted to Irish costs using the Purchasing Power Parity index.[14]

Additional healthcare use attributable to adverse events was identified from published studies and Irish unit costs were assigned.[44]

Assumptions

It was assumed that prescribed medicines were consumed (i.e. full adherence) and over-the-counter use was not included in the models. Health states only related to the adverse events of each PIP, so it was assumed that there was no significant differences in efficacy between each PIP and the appropriate alternative, and no significant adverse effects of the appropriate alternative. In the NSAID model, following an adverse event, it was assumed that individuals would be switched to an appropriate alternative. In the other models, it was assumed that individuals remained on therapy regardless of adverse events, due to unlikely attribution of the adverse events in the case of PPIs and dependence and withdrawal effects in the case of benzodiazepines. The effect of this assumption was assessed in structural sensitivity analysis.

Analytic methods

Economic impact of PIP relative to appropriate alternatives

Model structures were assessed for face validity by the research team and models were cross-validated by comparison to other published models concerning these therapeutic areas.[45] Models were validated by double-programming in Microsoft Excel 2010 (Microsoft Corp., Redmond, WA) to detect structural or coding errors, and extreme value testing and comparison of cohort traces between TreeAge Pro and Excel were also conducted.[45] Only the base case analyses were programmed in Excel. The models programmed in Excel are available from https://doi.org/10.6084/m9.figshare.5818251.v1, and TreeAge Pro model structures are included as Figures A2-4 in section 3, Appendix 2.

Base case models were run for the PIP and appropriate scenarios using point estimates for transition probabilities, costs, and utilities (as shown in Table A1 in Appendix 2) and results are presented as mean differences in costs, QALYs, and LYs. An incremental cost-effectiveness ratio (ICER) was also calculated for each PIP, indicating the expected additional cost per additional QALY in the PIP scenario relative to the appropriate alternative scenario. Differences in the total number of adverse events for the PIP scenario compared to the appropriate scenario were also determined. Uncertainty associated with imprecision of the parameter inputs was incorporated into the model using probabilistic sensitivity analysis (PSA) to allow 95% credible intervals (CIs) to be fitted (see Appendix 2, section 4 for further details). The impact of varying specific parameter inputs, including

costs and discount rates, was assessed in one-way deterministic sensitivity analyses.[14] Although not pre-specified, we also considered treatment adherence in one-way sensitivity analysis. Up to 20% non-adherence was assessed, which applied a reduction to medication costs and a reduction in the proportion within each state who were exposed to the medication and the associated relative risk of adverse events.

Cost-effectiveness of potential interventions

In the second stage of the analysis, each model was used to evaluate the cost-effectiveness of a potential intervention to reduce prescribing of each PIP drug by switching patients to the more appropriate alternative. This analysis was in the form of a value of implementation analysis,[46] and a new decision was framed between implementing an intervention to reduce PIP or usual care, as illustrated for NSAIDs in Figure A5 in Appendix 2, section 5. The intervention was delivered once at the beginning of the model to all individuals on a long-term NSAID and resulted in a proportion of these people being switched to paracetamol for the duration of the model time horizon. The intervention cost per person and effectiveness (i.e. the relative reduction in the proportion on a long-term NSAID) were varied to determine circumstances in which the intervention would be preferred to no intervention at a willingness-to-pay or cost-effectiveness threshold of €45,000/QALY (the conventionally used threshold in Ireland),[14] as well as thresholds of €20,000/QALY and €0/QALY. These results were plotted and this was then repeated for benzodiazepine and PPIs. Threshold analysis was conducted using effectiveness estimates from recent primary care trials targeting these PIP drugs which have no published economic evaluation to date to determine maximal costs at which each medicines optimisation intervention would be cost-effective (see section 5 of Appendix 2 for a description of these trials).[47–49]

Patient involvement

Patients were not involved in the conception, design, or conduct of this research.

Results

Economic impact of PIP relative to appropriate alternatives

Based on the study parameters used (Table A1), for all three models the PIP scenarios were dominated by the appropriate treatment scenarios (i.e. they generated higher costs and fewer QALYs). The incremental costs and QALYs were largest in the benzodiazepine model, where being on the PIP drug generated an average of €3,470 higher costs and 0.07 fewer QALYs per patient compared to the appropriate alternative scenario (Table 2). For costs, this was followed by patients on a long-term maximal dose PPI relative to those on a maintenance dose and then being on long-term NSAIDs compared to paracetamol. The QALY loss in the NSAID model was 0.07 QALYs and 0.01 QALYs in the PPI model. The excess adverse events in the PIP scenarios relative to the appropriate alternative scenarios are shown in Table A2 (Appendix 3). Uncertainty in the outcomes is illustrated in Figure 1 showing the distribution of cost and QALY differences for each model in the PSA. The 95% CIs generated from the PSA showed incremental costs and QALY losses were statistically significant for the NSAID (95% CI €415to €1,346 costs; -0.131to -0.026 QALYs) and benzodiazepine models (95% CI €2,434to €5,001 costs; -0.089to -0.047 QALYs). For the PPI model, the difference in costs and QALYs between maximal dose and maintenance dose prescribing was not statistically significant (95% CI -€69to €2,127 costs; -0.029to 0.003 QALYs).

In one-way deterministic sensitivity analysis, the PIP scenario was still dominated by the appropriate alternative scenario in each model across the range of values for the investigated parameters and the rankings of the models by incremental costs and QALYs did not change (see Table 3). Similarly, the post-hoc sensitivity analysis of treatment non-adherence showed a reduction in both incremental costs and QALYs with increasing non-adherence. Altering the NSAID model structure to assume no switch from the PIP drug to paracetamol after an adverse event (i.e. if patients remained on a long-term NSAID regardless of adverse events occurrence, consistent with the benzodiazepine and PPI models) resulted in a larger cost difference (€1,494, 95% CI €756to €2,493) and QALY difference (-0.11 QALYs, 95% CI -0.042to -0.203) between the PIP and appropriate scenarios. The distribution of cost and QALY estimates under this assumption is plotted in Figure A6 in Appendix 3.

Cost-effectiveness of potential interventions

Applying these models to determine the cost-effectiveness of potential interventions, the relationship between intervention cost, effectiveness and preferred option (intervention or usual

care i.e. no intervention) is represented graphically for each PIP drug in Figure 2. Additionally, see Figure A7 in Appendix 3 for an example interpretation of these plots. Taking estimates of effectiveness from recently published trials targeting these PIP drugs,[47–49] an intervention which reduces potentially inappropriate NSAID use by 49.8% would be cost-effective up to a cost of €1,971 per person at a CE threshold of €45,000. For an intervention that resulted in 23% discontinuation among benzodiazepine users, the corresponding threshold cost would be €1,480 and for a 55% reduction in potentially inappropriate PPI use it would be €831 (Table 4). The rank order of these potential interventions depended on the CE threshold used. Taking the extreme case of a CE threshold of €0 per QALY (i.e. willing to pay nothing additional for any QALY gain), cost-effectiveness would be achieved for interventions targeting NSAIDs, benzodiazepines, and PPIs up to costs per patient of €401, €798, and €544 respectively (Table 4).

Discussion

For the three PIP Markov models considered, the costs were greater and there were fewer QALYs where the potentially inappropriate medicine was prescribed compared to an appropriate alternative strategy (Table 2). For PPIs, the differences between the PIP and appropriate alternative did not reach statistical significance due to uncertainty in the risk of adverse events attributable to using maximal doses relative to maintenance doses (Figure 1). Of the three PIP drugs considered in this study, benzodiazepines for greater than four weeks compared to no sedative medicine had the greatest cost and QALY impact per patient (Table 2). In the evaluation of the cost-effectiveness of reducing PIP of these drugs, targeting long-term NSAIDs prescribing would be most cost-effective due to the published effectiveness of the intervention that was evaluated, though the ranking depended on the CE threshold used (Table 4).

Context of the literature

No other studies appear to have assessed the economic impact of PIP defined by STOPP beyond direct costs of medicines.[3] Several studies have quantified the costs of adverse events relating to drug classes included in this analysis, although in different settings.[50] For NSAIDs, the costs associated with no gastroprotection among older patients with peptic ulcer disease in the UK, the excess costs of GI injury among older US Medicaid patients, and the comparative costs of harm due to different NSAIDs have been evaluated.[6,9,51] Benzodiazepine drug interactions, although not potentially inappropriate benzodiazepine prescribing, were associated with significantly increased healthcare costs in a regression analysis of older patients,[7] while a further case-control study considered the attributable fall-related hospitalisation costs.[52] They estimated the cost of fall-related hospitalisations attributable to benzodiazepines in the Netherlands as €48.5 million, which is 18.9% of the total cost of fall-related admissions. An economic modelling study comparing benzodiazepines to cognitive behavioural therapy or no treatment among older adults with insomnia considering a time horizon of only one year also found substantial falls-related costs associated with sedative drug use.[8] While decision-tree analysis has been used to evaluate different PPI treatment strategies, including dose reduction, to manage oesophagitis,[53] the economic impact of adverse events or inappropriate prescribing of PPIs has not been evaluated. Comparisons with the present study are difficult, as previous research has often presented results at the population level rather than the incremental cost per person over an extended time horizon.

Despite many studies of interventions to address appropriateness of prescribing in older people in primary care, but few economic evaluations have been published.[3,10] The PINCER intervention in

English GP practices was cost-effective in both the in-trial economic evaluation and the model-based cost-utility analysis over a 5-year time horizon beyond the trial.[9,54] However there was uncertainty in the model-based results due to a lack of precise estimates of harm in the published literature for some of the prescribing/monitoring errors targeted.[9] An older study of clinical pharmacist advice to older US veterans on five or more medicines and their doctors reported a cost of $7.50-30 (€12-48) per patient per unit improvement in the Medication Appropriateness Index.[55] Other published economic evaluations have focussed on appropriate prescribing of only specific drug classes, such as benzodiazepines,[56,57] psychiatric medicines,[58,59] or cardiovascular medicines.[60] Of all of these interventional studies, only the PINCER trial conducted a model-based economic evaluation presenting results as an ICER (i.e. cost per QALY). Several recent trials of primary care interventions have successfully reduced PIP drugs. The OPTI-SCRIPT intervention involved academic detailing by a pharmacist and a computer decision support system for GPs in Ireland and resulted in a reduction in PIP, and in particular in long-term use of PPIs at maximal dosage.[47] The Scottish DQIP intervention employing education, informatics and incentives to assist GPs reviewing older patients' prescribing effectively decreased high-risk prescribing of NSAIDs and other medicines, and reduced the rate of hospitalisation for GI bleeding and heart failure.[48] Finally, the EMPOWER trial demonstrated that a patient empowerment intervention delivered through Canadian community pharmacies results in greater discontinuation of benzodiazepines than standard care.[49] The cost-effectiveness of these interventions has yet to be demonstrated through published economic evaluations, and hence this study illustrates the use of Markov models to assess the cost-effectiveness of reducing PIP and the resulting adverse events.

Strengths and limitations

This is the first study to quantify the economic impact of PIP in older people, considering not just the medication cost but also the adverse consequences. The use of Markov models allowed for available evidence on harm relating to PIP criteria from the published literature to be combined. The analysis also incorporated uncertainty in these estimates and a number of model validation steps were conducted. This study directly compared three types of suboptimal prescribing with distinct adverse effects on a common scale of costs and QALYs. Similarly it illustrates that the cost-effectiveness of potential interventions to improve prescribing in older people can be assessed using Markov modelling to capture the long-term consequences of medicines optimisation.

This study has several limitations. Only the principal adverse effects of each PIP were included to reduce the complexity and increase transparency of the models. Similarly, although prevalent

among older adults, we did not consider drug-drug and drug-disease interactions or exacerbations of underlying conditions within the models. A number of model assumptions were applied to address this study's aim. Firstly, as the STOPP criteria refer to drug classes, we used pooled estimates for each class for the risk of adverse effects to provide the average economic impact of each PIP, and heterogeneity within drug classes was beyond the scope of this study. Similarly we did not consider strategies that modify risks, such as gastroprotection with NSAIDs to prevent GI adverse events with NSAIDs. Secondly the cohort under consideration were 65 year olds, assumed to be continuous users of each PIP, and in the intervention evaluation, the reduction in PIP was assumed to be sustained over the full time horizon. In reality, patients may spend some time exposed and unexposed, however, these assumptions allowed comparison of the overall effects of each PIP. We considered treatment adherence in sensitivity analysis and although adherence to these medication classes is likely to be high given their symptomatic effects, adherence be lower may in some cases than is considered here. The analyses was performed on a cohort basis to assess the average costs and effects, which does not reflect the variability of these outcomes among individuals, where some patients may incur large costs and have a greater reduction in QALYs. Heterogeneity was also not considered, as the research did not aim to evaluate how the economic impact may vary among patient subgroups. Further research should determine the extent to which differences in individual patient characteristics may alter the economic impact of PIP. This analysis focussed only on adverse effects of prescribing deemed to be potentially inappropriate, however appropriate alternative were selected on the basis of similar effectiveness and limited adverse effects. Although these types of prescribing are generally regarded as inappropriate for older adults, there may be circumstances where patients and their doctors weigh the benefits and harms and decide that the "inappropriate" prescription is optimal for them individually.

Implications for policy and practice

Trial-based economic evaluations may not always be informative for policy-maker decisions due to, for example, relevant comparators not being included, an insufficient time horizon, or measurement of intermediary endpoints (e.g. serum cholesterol) or process measures (e.g. PIP) rather than final outcomes.[44] Modelling approaches can overcome these weaknesses, by allowing all relevant evidence to be synthesised, incorporating alternative treatments not directly compared in a trial, and extrapolating beyond the duration of the trial to assess long-term outcomes.[12] Adoption of economic modelling approaches could increase the number of informative economic evaluations of prescribing safety interventions, such as in the PINCER trial.[9] Such methods may be

particularly useful in evaluating services to improve other aspects of medicines use where the benefits may not manifest during the period of a trial, for example, interventions to improve adherence to preventative medicines.[61] Future trials of new or expanded services should conduct robust economic evaluations and include long-term consequences to inform policy-makers' decisions on implementation and funding allocation. Cost-utility analyses presenting results as cost per QALY are most informative, allowing policy-makers to compare interventions and make funding decisions across therapeutic domains. Model-based approaches, as illustrated here, are an effective method to produce these estimates and evaluate interventions which affect outcomes across physiological systems.

Prescribing of potentially inappropriate medicines has significant economic implications, and interventions to reduce PIP are likely to be cost-effective if implemented into primary care for older people. The 95% CIs for cost and QALY differences in the PPI model both included zero, which, similar to the PINCER trial, was due to uncertainty relating to the adverse effects.[9] This indicates that more information is needed on the safety of maximal compared to maintenance doses,[62] and therefore these results should not deter efforts to deprescribe PPIs where their use is potentially inappropriate.[2,47] As illustrated in Table 4, the CE threshold being used by policy-makers (i.e. the cost they are willing to pay for a QALY) can influence which interventions are funded. Placing a greater monetary value on each QALY will favour interventions that improve quality and quantity of life over those that reduce healthcare costs. While an explicit CE threshold exists for new drugs in the Irish health system, it is less clear whether the same applies to other interventions, such as those to improve prescribing.[63] It may be that a lower CE threshold applies to these, for instance, if no additional funding is available for medicines optimisation services and only cost-saving interventions are acceptable to decision-makers. Using a different CE threshold may alter healthcare decisions and potentially result in less net benefit for patients across the health system.[63]

Conclusions

Potentially inappropriate prescribing of benzodiazepines and NSAIDs carry a statistically significant cost, to both the health system and patients, and there is an economic case for implementing effective interventions to improve prescribing of these medications for older people. Maximal dose PPI use is highly prevalent but evidence of harms is less certain, and so further studies should consider whether continuing maximal dose PPI is associated with increased risks compared to maintenance dose prescribing in order to establish whether targeting this is an efficient use of

resources. Future research should also evaluate which patient subgroups inappropriate medication use have the greatest economic impact on, and thus, which patients would most benefit from prescribing optimisation interventions to maximise cost-effectiveness.

Data sharing: Markov models coded in Microsoft Excel are available at https://doi.org/10.6084/m9.figshare.5818251.v1 and data inputs are included in the technical appendix (Table A1, Appendix 2).

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Transparency statement: FM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Figures

Figure 1 Incremental costs and utilities for PIP compared to appropriate from probabilistic sensitivity analysis for each model (northwest quadrant)

Figure 2 Cost and effectiveness at which interventions would be cost-effective at a cost-effectiveness threshold of €45,000 per QALY for a) benzodiazepine, b) PPI, and c) NSAID models

Tables

Table 1 Description of included criteria from the Screening Tool for Older Persons' Prescriptions (STOPP)

Potentially inappropriate prescription	Comparator	Prevalence [2]	Adverse events represented
NSAID >3 months	Paracetamol	4.1%	Dyspepsia Gastrointestinal bleed Myocardial infarction
Benzodiazepine >4 weeks	No sedative medication	4.3%	Hip fracture Other fall injuries
PPI maximal dose >8 weeks	Maintenance dose PPI	23.6%	Hip fracture *Clostridium difficile* infection

Table 2 Cost, effect, and ICER outputs for PIP compared to appropriate scenarios for each model

Strategy	Cost, €	Incr. Cost, € (95% CI)	QALYs	Incr. QALYs (95% CI)	ICER, €/QALY	LYs	Incr. LYs
NSAID model							
Paracetamol >3m	2,603		8.72			11.54	
NSAID for >3m	3,409	806 (415 to 1,346)	8.65	-0.07 (-0.131 to -0.026)	-11,511	11.46	-0.08
Benzodiazepine model							
No benzodiazepine	25,158		8.78			11.69	
Benzodiazepine ≥4 wks	28,628	3,470 (2434 to 5001)	8.72	-0.07 (-0.089 to -0.047)	-52,672	11.65	-0.04
PPI model							
Maintenance dose >8 wks	24,831		8.82			11.70	
Maximal dose >8 wks	25,819	989 (-69 to 2127)	8.81	-0.01 (-0.029 to 0.003)	-85,279	11.68	-0.02

Abbreviations: CI, credible interval; ICER, incremental cost-effectiveness ratio; LYs, life years; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; QALYs, quality-adjusted life years.

Table 3 One way deterministic sensitivity analysis results

	NSAID model	Benzodiazepine model	PPI model
	Incremental effect (QALYs)		
Outcome discount rate			
0	-0.157	-0.175	-0.035
0.02	-0.111	-0.115	-0.022
0.04	-0.082	-0.079	-0.014
0.06	-0.061	-0.056	-0.010
Non-adherence to treatment			
10%	-0.064	-0.059	-0.011
20%	-0.058	-0.052	-0.010
	Incremental cost (€)		
Costs discount rate			
0	1,145.45	6,497.62	1,767.79
0.02	984.56	4,978.65	1,379.78
0.04	858.79	3,893.76	1,099.22
0.06	758.79	3,108.09	893.40
Inpatient cost of *C. difficile*			
€4,000.00	-	-	961.63
€6,398.72	-	-	996.79
€8,797.45	-	-	1,031.94
€11,196.17	-	-	1,067.09
PIP drug cost[a]			
Low	349.20	3,016.20	478.15
High	1,125.73	4,474.65	2,166.44
Non-PIP drug cost[b]			
Low	1,192.38	-	1,673.52
High	660.57	-	477.64
Non-adherence to treatment			
10%	740.56	3,117.12	900.42
20%	672.11	2,765.54	810.45

[a] PIP drug cost range (€) NSAID: 74.82-202.00, benzodiazepine: 38.96-164.16, PPI: 117.12-261.60.

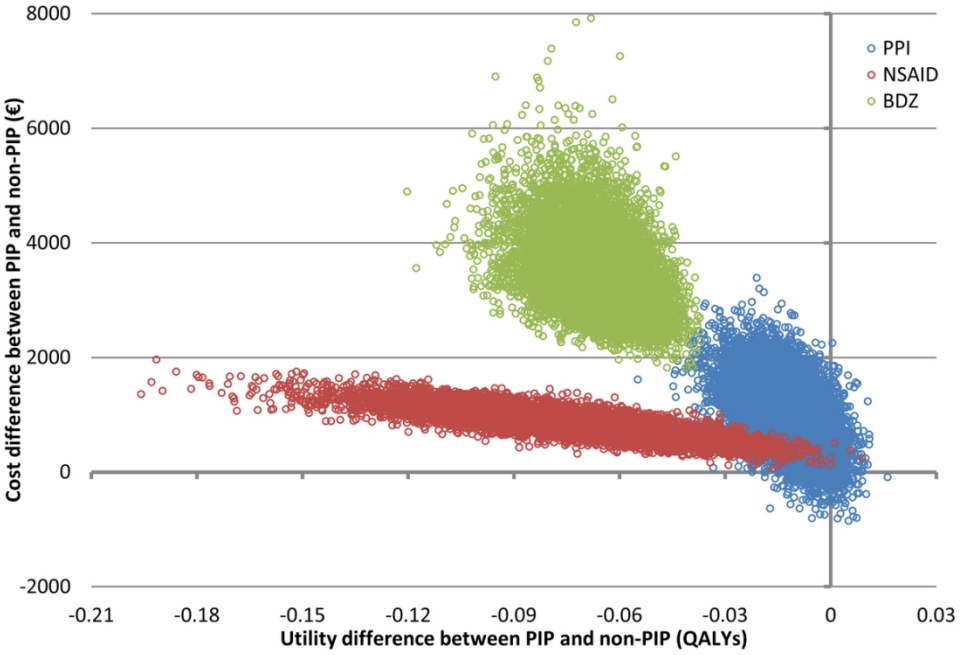
[b] Non-PIP drug cost range (€) NSAID: 38.40-120.00, PPI: 56.56-160.80.

Table 4 Threshold values across cost-effectiveness thresholds for intervention cost at levels of effectiveness from published trials

	NSAIDs	**Benzodiazepines**	**PPIs**
Intervention effectiveness (risk reduction)[a]	0.498	0.23	0.55
	Threshold cost (€) at published intervention effectiveness[a]		
WTP (€ per QALY)			
0	401	798	544
20,000	1099	1101	671
45,000	1971	1480	831

Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; QALY, quality-adjusted life year; WTP, willingness-to-pay.

[a] Effectiveness estimates used were taken from Dreishulte et al. for NSAIDs,[48] Tannenbaum et al. for benzodiazepines,[49] and Clyne at al. for PPIs.[47]



Incremental costs and utilities for PIP compared to appropriate from probabilistic sensitivity analysis for each model (northwest quadrant)

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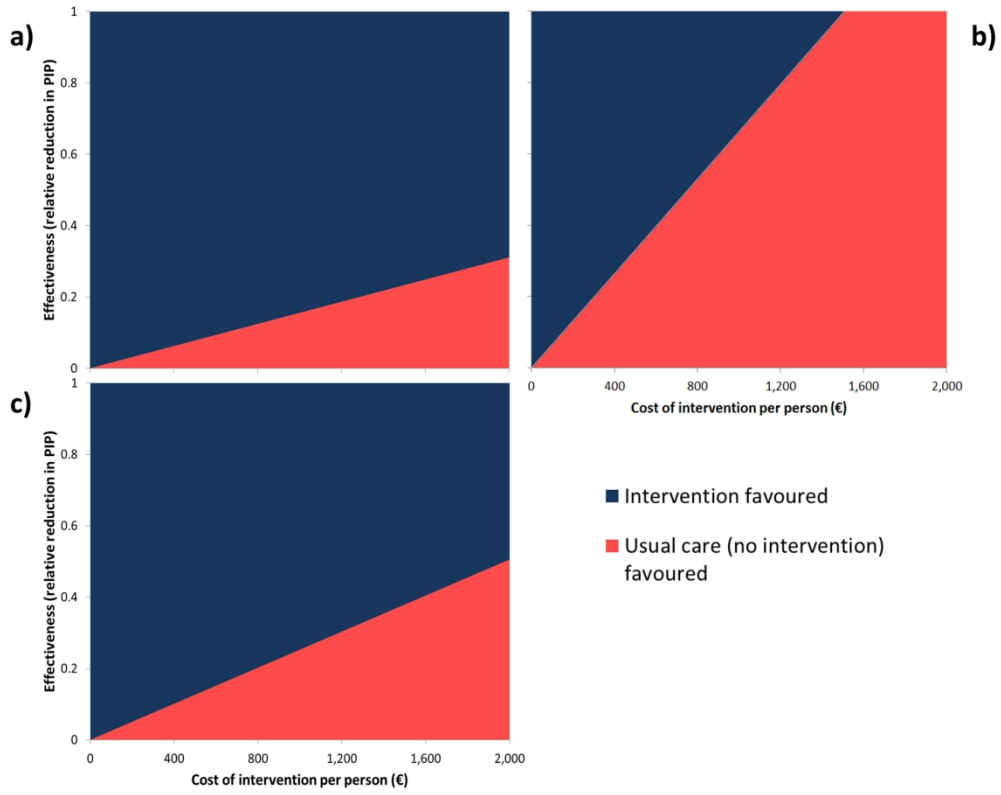

Cost and effectiveness at which interventions would be cost-effective at a cost-effectiveness threshold of €45,000 per QALY for a) benzodiazepine, b) PPI, and c) NSAID models

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Appendix 1 – CHEERS checklist

Section/item	Item No	Recommendation	Reported on page No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 4, paragraph 1
		Present the study question and its relevance for health policy or practice decisions.	Page 4, paragraphs 2-3
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 5, paragraph 1
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 5, paragraph 1
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 5, paragraph 1
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 5, paragraph 1 and Table 1
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5 paragraph 1
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 5, paragraph 1
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 5, paragraph 1 and Page 6, paragraphs 2-3
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Technical appendix, section 2.1
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Page 6, paragraph 2 and Technical appendix, section 2.3
Estimating resources and costs	13a	*Single study-based economic evaluation:*Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	

	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 6, paragraph 3 and Technical appendix, section 2.2
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 6, paragraph 3
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 5, paragraph 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 6-7 (Assumptions) and Technical appendix, section 1
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 7-8 (analytical methods) and Technical appendix, section 3-5
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Technical appendix, Table A1 and Section 2
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 9, paragraph 1 and Table 2.
Characterising uncertainty	20a	*Single study-based economic evaluation:*Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 9, paragraph 1 and 2, Figure 1 and Figure A7
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not	N/A

		reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 11-13
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 15
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 15

Appendix 2 - Technical Appendix

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1 Description of model structures and states

The states included in each model capture the possible consequences for a patient with a potentiall inappropriate prescription (PIP) and the typical resource use and increased risks following an event are described. The same model structures were used for both the PIP and non-PIP scenarios, with the only differences being transition probabilities and cost of the PIP or non-PIP treatment.

1.1 NSAID model

All patients start in the 'Well (no previous event)' state and remain here until they have a gastrointestinal (GI) event (dyspepsia or GI bleed), a myocardial infarction (MI), or die (top, Figure A 1). Patients are on diclofenac 75mg twice daily in the PIP arm or paracetamol 1,000mg four times daily in the non-PIP arm. In the non-PIP arm, the transition probabilities reflect the rates of the adverse events in the general non-steroidal anti-inflammatory drug (NSAID) non-user population, and in the PIP arm, the relative risk in NSAID users was applied to these probabilities.

Patients can transition to the 'Dyspepsia' state where individuals have persistent dyspepsia causing GI discomfort requiring consultation with a doctor and so they attend their general practitioner (GP) for an extra visit, are switched from diclofenac to paracetamol and receive a prescription for a proton pump inhibitor (lansoprazole 15mg once daily for four weeks). They return to the baseline (non-PIP) risk of further dyspepsia and if no further event occurs in the following cycle, they transition to the 'Well, GI event history' state.

Patients who transition to the 'GI bleed' state in this state attend the emergency department (ED), are admitted to hospital for investigation and management of upper GI bleeding, are switched from diclofenac to paracetamol and receive a prescription for lansoprazole 15mg once daily for four weeks. After discharge, they are expected to have additional healthcare use as a result of their GI bleed, namely two GP visits and two outpatient department (OPD) visits.[1,2] As with dyspepsia, they return to baseline risk of a further GI bleed and transition to the 'Well, GI event history' state if they have no further event in the following cycle. In the 'Well, GI event history' state, patients' therapy has been switched from diclofenac to paracetamol, so the cost of medication (paracetamol) and transition probabilities for further GI events or an MI from this state is equal in both the PIP and non-PIP arms.

Patients transition to the 'MI' state following an MI and remain here for one cycle unless they have a further MI in the following cycle. Patients who have an MI incur inpatient treatment costs, are switched from diclofenac to paracetamol and commence medications for secondary cardiovascular prevention. They also have an additional 11 OPD visits and attend their GP an extra 8 times in the

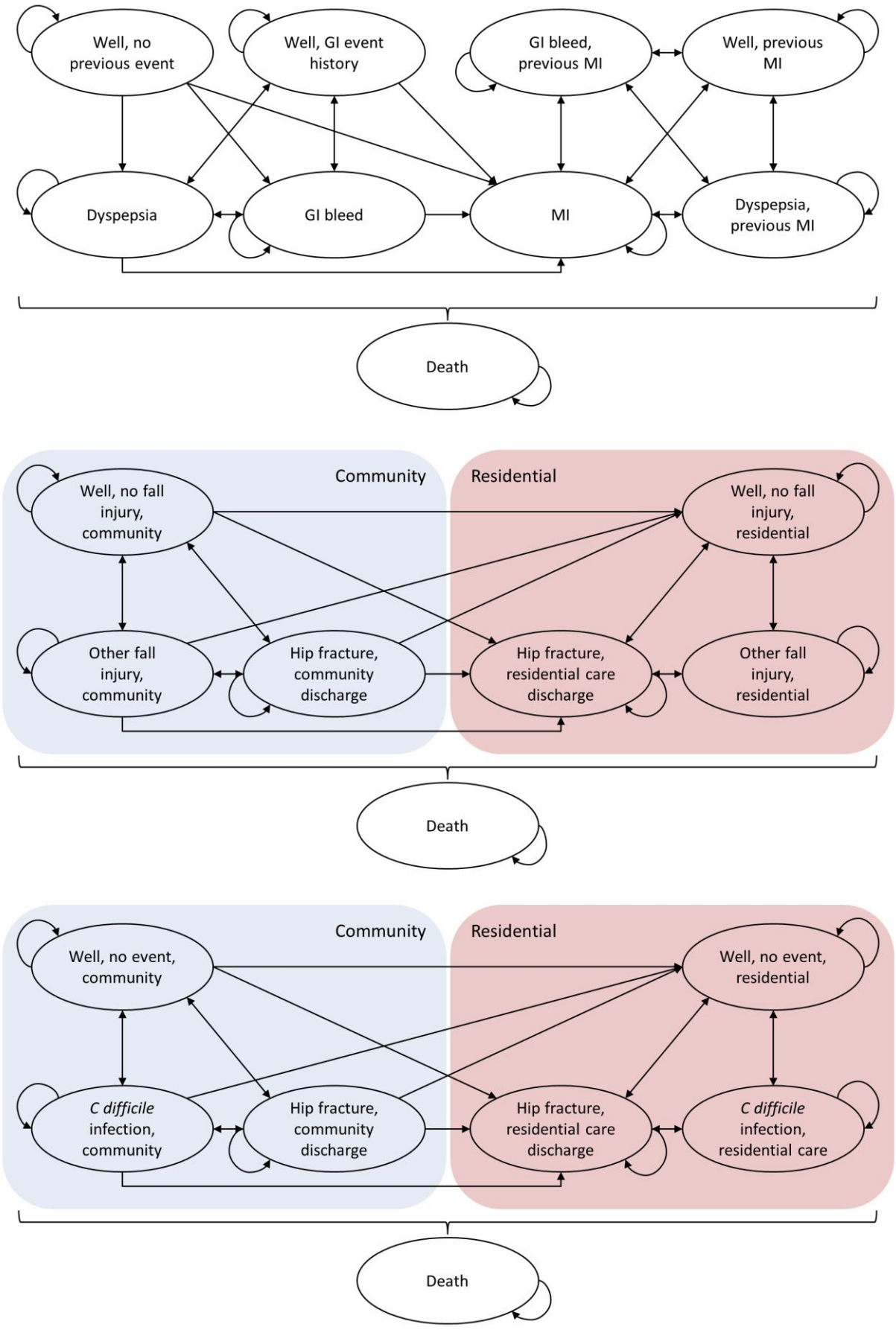

Figure A 1 Structures for NSAID (top), benzodiazepine (middle), and PPI (bottom) Markov models

year of an MI.[3] During this year patients are also at increased risk of a further MI.[4] If no event occurs in the subsequent cycle then patients transition to the 'Well, previous MI' state, where the probability of a subsequent MI falls, although it remains higher than in patients with no previous MI.[4] Patients in any 'previous MI' state incur the costs of attending two extra OPD appointments and two GP appointments per year,[3] as well as the cost of secondary preventive medicines and paracetamol.

1.2 Benzodiazepine model

All patients start in the 'Well, no fall injury, community' state as the cohort is community-dwelling and are assumed to have had no fall injury in the previous 12 months (middle, Figure A 1). The only cost incurred by patients in this state is the cost of the PIP medication, diazepam 5mg twice daily in the PIP arm, whereas no pharmacotherapy is prescribed in the non-PIP arm. Patients in the PIP arm remain on this medication with its associated cost and increased adverse events risk throughout the model i.e. no therapy switch occurs after an adverse event. From this state, a transition can occur following a hip fracture or some other fall injury that a patient seeks healthcare for. Hip fractures were divided into (i) those where the patient returns home and (ii) those which result in the patient being permanently admitted to a nursing home setting. Other events that can occur independently of falls are death and admission to a nursing home.

On having a hip fracture, patients transition to one of the two hip fracture states, depending on where they are discharged to following this event and remain here for one cycle, unless they suffer a further hip fracture. All hip fracture patients present at an ED, are admitted as inpatients and are discharged either back to the community or to a residential care setting. After discharge, hip fracture patients attend an average of 9 additional OPD appointments and have an excess of 10 visits to their GP.[5] For those discharged to the residential setting, there is the additional cost of nursing home residence. For 12 months following a hip fracture patients are at an increased risk of a further fall due to their recent injurious fall.[6] If they have no hip fracture or other fall injury in the following cycle, they transition back to the 'Well, no fall injury' state (either community or residential) and return to baseline fall risk.

All patients with a fall injury requiring healthcare that is not a hip fracture (such as bruising, soft tissue injuries or other types of fractures) transition to the 'Other fall injury' state. The costs incurred in this state are based on a weighted average of the prevalence of different injury types and typical healthcare use taken from an Irish costing study.[7] Half of patients with other falls injuries have one additional visit to their GP, 22% attend an ED, are not admitted and are referred

to their GP for a follow-up visit. Twenty percent attend ED with a non-hip fracture, are admitted as inpatients, and are discharged to community where they have 9 additional OPD visits and 6 extra GP visits.[5] The remaining 8% attend ED with other fall injuries, are admitted as inpatients and following discharge, are referred for one OPD visit and one GP visit for follow-up.[8] The only difference between community and nursing home setting is the additional cost of nursing home residence. As with the hip fracture states, patients remain in this state for one cycle unless they suffer another fall injury and are at an increased risk of a further fall while in this state.

Patients from all of the community-based states transition to the 'Well, no fall injury, residential' state based on the annual probability of being admitted to a nursing home. This background probability of nursing home admission is included as otherwise the number of admissions attributed to hip fracture in benzodiazepine users would be overestimated. Patients also transition to this state in the cycle following a hip fracture which results in permanent nursing home admission, or if they are nursing home residents who suffer a hip fracture or other fall injury. As only permanent admissions are represented in this model, no transitions occur from residential states back to community states.

1.3 PPI model

The model structure (bottom, Figure A 1) is similar to the benzodiazepine model. All individuals start in the 'Well, no event, community' where the only resource use is cost of the PIP or non-PIP medication (i.e. maximal dose proton pump inhibitor (PPI) or maintenance dose PPI). Patients in each arm remain on these medications, with their associated costs and increased adverse events risk, throughout the model i.e. no therapy switch occurs after an adverse event. A number of events can then occur, those that are affected by PIP exposure (*Clostridium difficile* infection and hip fracture) and those that are unaffected (death and admission to a nursing home). Similarly, following a transition to a residential state, patients remain there and no transition back to community can occur.

Following a hip fracture, patients transition to one of the 'Hip fracture' states (again depending on the setting they are discharged to) and remain in this event state for one cycle, unless they suffer a further hip fracture. Regarding healthcare utilisation, the same pattern that applied to this state in the benzodiazepine model was used here, including the additional cost of nursing home care for residential states.

Patients who develop *C. difficile infection* transition to the '*C difficile* infection' state for one cycle where the healthcare resource use is the cost of inpatient management attributable to the

infection, as community-dwelling patients aged 65 years or over are likely to be admitted as a result of an infection.[9] No further healthcare costs are incurred, and there is no increased risk of recurrence following a case (as recurrent cases were included in the baseline probability used) or being in a residential setting.

2 Sources of model inputs

The parameter inputs used in each model, along with the sources for these and the distributions used in the probabilistic sensitivity analysis are provided in Table A 1. The sources of each input are described in more detail below.

2.1 Transition probabilities

2.1.1 NSAID model

The probability of dyspepsia for non-NSAID users and the relative risk associated with NSAID use were taken from a meta-regression of trials and large exposure observational studies.[10,11] In these studies, a hypothesis was stated a priori that the prevalence in trial placebo groups would be lower than in the general population due to a selection bias in trials enrolling healthier patients. Therefore the probability was obtained by applying the relative risk to the prevalence from included NSAID versus NSAID trials. For GI bleeds, a pooled incidence rate in people aged 65 years and over from a review of epidemiological studies was used to calculate the probability.[12] Higher estimates have been reported, however these sources included NSAID users in the study populations. The risk of GI bleeds associated with naproxen and other NSAIDs was taken from a meta-analysis of randomised controlled trials.[13] The same risk of death following a GI bleed was applied to NSAID users and non-users,[14] and a UK hospital based study was the source of age-specific excess mortality estimates.[15] The baseline probability of an MI was estimated from an observational study of NSAID non-users aged 65 years and over and applied to all states with no previous MI,[16] and the probability of a further MI in the 12 months after an event was taken from a recent English population-based study.[4] This study was also the source for the probability of a subsequent MI more than one year post-MI which was applied to the previous MI states.[4] The pooled relative risk of MI on NSAIDs in the PIP arm was taken from the same meta-analysis of trials which yielded the effect on GI bleeds.[13] Probability of death in the year following an MI was taken from a study which provided the cumulative in-hospital and post-discharge mortality rate in a French cohort.[17] The long-term increase in relative mortality post MI was taken from a population-based study and applied to background mortality rate.[4] As this incorporated deaths from further MIs, the mortality from re-infarction was subtracted from this.

The increased risk of dyspepsia, GI bleeds, and MI in the PIP arm only applied to patients in the Well, no previous event state as any transition from this state following an event resulted in a switch from an NSAID to paracetamol. This switch from PIP to the non-PIP option after an adverse event was only applied to the NSAID model, not the benzodiazepine or PPI models. In the former

case patients/doctors may be reluctant to stop the benzodiazepine or it may be felt that stopping would pose a greater risk than continuing in older patients,[18] and for the latter a causal link between PPI exposure and adverse events is unlikely to be made.[19] The impact of relaxing this structural assumption for the NSAID model was assessed in sensitivity analysis.

2.1.2 Benzodiazepine model

This model only concerns falls which result in costs to the health service, therefore falls which result in no injury or falls injury which people do not seek healthcare for were excluded. The probability of a hip fracture was taken from a study reporting number of cases by age group from Irish hospital inpatient data.[7] This source was used in preference to another based on Irish data which provided similar estimates but which were presented separately by sex.[20] The estimate of the proportion of patients who are permanently admitted to a nursing home following hip fracture was taken from a cohort study in Northern Ireland which followed up patients one year post-fracture.[21] For the probability of other fall injuries, the probability of hip fracture was subtracted from the age-specific probability of an injurious fall.[22–25] The same probabilities for hip fracture and other fall injuries were applied to community and residential states. As no trials or meta-analysis of trials have been powered to detect the effect of benzodiazepines on falls, the estimate from the most recent meta-analysis of observational studies was used,[26] and two further meta-analyses had similar results.[27,28] An increased risk of a fracture or other fall injury was applied in the 12 months following a fracture or fall and this effect was taken from a meta-analysis of observational studies which reported the relative risk of a fracture in the year following a fracture.[6] The only attributable mortality included in this model was due to hip fracture,[29,30] and the relative hazard of mortality one year post fracture from a meta-analysis was applied to the all-cause mortality rate.[31] Background age-specific probability of nursing home admission (independent of hip fracture) was calculated from Irish data on the prevalence of nursing home residence.[32]

2.1.3 Proton pump inhibitors model

The probability of hip fracture, the joint probability of being admitted to a nursing home in the 12 months following a hip fracture, the relative mortality hazard in the 12 months following hip fracture, and the probability of admittance to a nursing home independent of hip fracture were taken from the same sources as the benzodiazepine model. The probability of *C. difficile* infection was based on the Irish national clinical guidance which reports the incidence in 2013.[9] The adjusted hazard ratio for mortality following *C. difficile* infection was taken from a propensity score matched-pairs analysis.[33] The source used for the increased risk of hip fracture in the PIP arm

relative to the non-PIP arm was a systematic review and meta-analysis of observational studies,[34] while the dose effects of PPIs on *C. difficile* infection was taken from a single observational study which reported this.[35] The inputs used were the risks in maximal dose PPI users relative to non-users divided by the risks in maintenance dose users relative to PPI non-users. For both fractures and *C. difficile*, there was no evidence of a significant difference between maximal dose and maintenance dose PPI users as reflected by overlapping confidence intervals, and in the case of hip fracture, the Cochran Q test for non-combinability. While this could not be accounted for in the point estimate, this was incorporated into the probabilistic sensitivity analysis when distributions were specified for these estimates.

2.2 Costs

The inpatient cost for managing a GI bleed was taken from the Health Service Executive (HSE) National Casemix Programme Ready Reckoner report which provides the average cost per case for various DRGs for 39 national hospitals participating in the National Casemix Programme.[36] This was consistent with the findings of an Irish study of patients admitted from a hospital ED with low-risk non variceal GI bleeding.[37] A study conducted in a large Irish hospital used a micro-costing approach was the source for the inpatient costs of a myocardial infarction.[38] Inpatient costs for hip fracture were taken from a previous economic evaluation which reported Irish cost data,[20] while for other fall injuries, the cost input was an average of the resource use weighted by the prevalence of different types of injuries, using Irish hospital costs for inpatient stays.[7] No Irish inpatient data was available on costs of *C. difficile* infection however a European systematic review provided several estimates, of which costs from a Northern Irish study were used and the impact of using other estimates from this review were examined in sensitivity analysis.[39,40]

For other healthcare utilisation, the typical excess number of OPD and GP visits post-discharge were taken from published case-control studies for GI bleeds,[1,2] MI (both in the first and in subsequent years post-event), [3] hip and other fractures,[5] and other non-fracture fall injuries.[8] The average cost of an OPD visit was taken from the HSE National Casemix Programme,[36] and cost per GP visit was calculated based on the average annual payment by the health service to GPs per General Medical Services (GMS) patient and the mean number of visits per patient.[41,42] The cost of attending an ED used was the average reported by the National Casemix Programme.[36] Medication costs were calculated using 2014 data from the HSE Primary Care Reimbursement Service (HSE-PCRS) for ingredient costs and a pharmacist dispensing fee of €5 was added for each month's supply to reflect the cost to the health service. As each PIP indicator refers to a drug class,

the medication most frequently prescribed in cases of PIP in a recent Irish population study was used i.e. diclofenac, diazepam and lansoprazole for NSAIDs, benzodiazepines and PPIs respectively.[43] The cost of one year's supply of one defined daily dose (DDD) per day was used. The costs of these PIP and non-PIP medications were varied in one-way sensitivity analyses over the range of costs of different drug molecules. In probabilistic sensitivity analysis, higher variance was included in the distributions for PPI costs as these are subject to continued price reductions through reference pricing.[44] The cost of secondary preventive medications (aspirin 75mg, atenolol 50mg, ramipril 5mg, and simvastatin 20mg) was included for the MI and post-MI states. The annual cost to the health service for a person in nursing home residence was determined from 2014 data on HSE spending on the Nursing Home Support Scheme and the number of individuals funded through this.[45]

2.3 Utilities

The preferences used in weighting for QALYs can be directly measured using rating scale, standard gamble or time trade off (TTO) methods. As these methods can be time-consuming and complex to use, an alternative is multi-attribute utility systems such as the EQ-5D-3L. Firstly, patients describe the health state they are in using a generic descriptive system of attributes which captures all important dimensions of the state. Secondly, valuations for each of these attributes derived from the general public are combined to determine an overall quality for the health state. In the EQ-5D-3L, five attributes are included (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and for each of these three response levels are defined. A valuation or tariff is estimated for all possible health states (3^5 = 243) by a large sample of individuals valuing each state using the time trade off method. Coefficients are derived for each level of each attribute using regression, which are combined as a decrement from a utility of 1.0 to give a utility for each state.

2.3.1 NSAID model

Disutilities for dyspepsia and GI bleeds were based on directly elicited utilities,[46,47] and the typical period of time patients would suffer symptoms for.[48] This is consistent with previous economic modelling methods,[49] and the disutility was calculated as follows:

$$(1 - utility\ of\ health\ state) \times \frac{Time\ in\ health\ state\ in\ days}{365\ days}$$

The disutility in the year following an MI was taken from a study reporting the annual utility loss associated with various cardiovascular events adjusted for patient characteristics using regression methods.[50] As evidence was conflicting regarding whether there was a long-term quality of life

impact following an MI,[51,52] the most conservative estimate in the literature of MI disutility in subsequent years was applied, and a wide distribution was used in probabilistic sensitivity analysis to reflect the uncertainty around this value.[53]

2.3.2 Benzodiazepine model

The most robust estimates of utility loss following fractures are from two systematic reviews and one Swedish study which uses three different scenarios to analyse the disutility in the 12 months following various fracture types and were similar across these studies.[54–56] The disutility for hip fracture was taken from the systematic review which included the greatest number of studies, and the utility loss in the year following a wrist fracture from this study was applied to the other fall injury state.[56] A disutility was applied to all residential states, consistent with previous economic models relating to hip fractures, on the basis that individuals who are institutionalised are likely to have some impairment in the dimensions captured by the EQ-5D such as mobility, self-care, or usual activities.[57,58] The input used was based on the utility difference between carers of Alzheimer's disease patients in the community and in nursing home residence.[59]

2.3.3 PPI model

The disutility of hip fracture and residence in a nursing home were the same as those used in the benzodiazepine model. The disutility of a case of *C. difficile* does not seem to have been directly elicited in any study using the EQ-5D or time trade off methods. The annual utility loss due to *C. difficile* was based on the utility of being hospitalised and the likely duration of hospital stay, calculated using the equation above.[60,61]

Table A 1 Point estimates for each parameter input and distributions used in probabilistic sensitivity analysis

Parameter description	Value	Distribution	Source
NSAID model			
Transition probabilities			
Probability of dyspepsia in non-NSAID users	0.0497	Beta (4,058, 75,513)	[10,11]
Probability of GI bleed in non-NSAID users	0.0013	Beta (99.71, 76,601.91)	[12,13]
Probability of death following GI bleed by age group		Beta	[64]
60-79	0.11	(156, 1,265)	
80+	0.2	(174, 698)	
Probability of an MI in non-NSAID users	0.0082	Beta (419, 50775)	[16]
Probability of an MI in the 12 months following an MI	0.064	Beta (2339.94, 34221.56)	[4]
Probability of an MI in subsequent years after an MI	0.0143	Beta (1378.65, 95030.28)	[4]
Probability of death following an MI	0.097	Beta (209, 1942)	[17]
Probability of death by age group			
65-69	0.0121		[65]
70-74	0.0198		
75-79	0.0340		
80-84	0.0644		
85+	0.1495		
Effect			
Relative risk of dyspepsia in long-term NSAID users	1.4	Log-normal (0.336, 0.126)	[10,11]
Relative risk of GI bleed in long-term NSAID users	3.07	Log-normal (1.122, 0.114)	[13]
Relative risk of MI in long-term NSAID users	1.53	Log-normal (0.425, 0.174)	[13]
Relative risk of death in people >1 year post-MI	2	Log-normal (0.693, 0.088)	[4]
Utility			
Utility of being in well state		Beta	
65-74	0.77	(129.13, 38.57)	[66]
75+	0.74	(108.51, 38.13)	
Utility decrement in 12m following dyspepsia	0.0325	Gamma (129.13, 38.57)	[46,47,49]
Utility decrement in 12m following GI bleed	0.0433	Gamma (108.51, 38.13)	[46,47,49]
Utility decrement in 12m following MI	0.055	Gamma (74.37, 1352.24)	[50,51]
Annual utility decrement >12m post-MI	0.012	Gamma (4, 333.33)	[51–53]
Costs			
Cost of NSAID treatment	149.64	Gamma (100, 0.668)	[67]
Cost of paracetamol treatment	97.68	Gamma (100, 1.024)	[67]
Cost of managing dyspepsia	152.64	Gamma (100, 0.655)	[67]
Cost of managing a GI bleed	4,983.68	Gamma (44.44, 0.009)	[36,37,67]
Cost of managing an MI	9,856.67	Gamma (100, 0.010)	[3,36,38]
Cost of a previous MI	819.56	Gamma (100, 0.122)	[3,67]
Benzodiazepine model			
Transition probabilities			
Probability of an injurious fall requiring healthcare utilisation		Beta	[22–25]
65-79	0.0476	(95, 1,905)	
80+	0.1	(200, 1,800)	
Probability of a hip fracture		Beta	[7]
65-69	0.0014	(197, 140,517)	
70-74	0.0031	(357, 114,804)	
75-79	0.0066	(597, 89,858)	

Parameter description	Value	Distribution	Source
80-84	0.0152	(961, 62,263)	
85+	0.0247	(1,071, 42,289)	
Probability of being in nursing home at 12m following a hip fracture	0.11	Beta (224, 1,810)	[21]
Probability of being admitted to nursing home in general population			[32]
		Beta	
65-69	0.0021	(301, 143,095)	
70-74	0.0033	(393, 118,759)	
75-79	0.0065	(601, 91,865)	
80-84	0.0151	(980, 63,904)	
85+	0.0241	(1,093, 44,254)	
Effect			
Relative risk of an injurious fall in long-term benzodiazepine users	1.553	Log-normal (0.440, 0.043)	[26]
Relative risk of injurious fall in 12 months post-fall injury	2.0	Log-normal (0.693, 0.039)	[6]
Relative hazard of death in 12 months following a hip fracture relative to people without fracture	3.26	Log-normal (1.182, 0.062)	[31]
Utility			
Utility decrement in 12m following a hip fracture	0.203	Gamma (209.33, 1,031.2)	[55,56]
Utility decrement in 12m following other fall injury	0.06	Gamma (22.13, 368.79)	[55,56]
Utility decrement of being resident in nursing home	0.06	Gamma (0.58, 9.72)	[57–59]
Costs			
Cost of benzodiazepine treatment	77.92	Gamma (100, 1.283)	[67]
Cost of hip fracture	17,394.47	Gamma (385.34, 0.022)	[5,20,67]
Cost of other fall injury	2,782.39	Gamma (25, 0.009)	[5,7,8,67]
Cost of residence in nursing home	42,670.00	Gamma (9,407.98, 0.220)	[45]
PPI model			
Transition probabilities			
Probability of having *C. difficile* infection	0.00358	Beta (1839, 511,848)	[9]
Effect			
Relative risk of hip fracture in maximal dose PPI users relative to non-users	1.462	Log-normal (0.380, 0.097)	[34]
and maintenance dose PPI users relative to non-users	1.247	Log-normal (0.221, 0.050)	
Relative risk of *C. difficile* infection in maximal dose PPI users relative to non-users	2.349	Log-normal (0.854, 0.140)	[35]
and in maintenance dose PPI users relative to non-users	1.735	Log-normal (0.551, 0.114)	
Relative hazard for death in 12m post *C. difficile*	1.23	Log-normal (0.207, 0.089)	[33]
Utility			
Utility decrement in 12m post *C. difficile*	0.026	Gamma (0.530, 20.38)	[60,61,63]
Costs			
Cost of max dose PPI treatment	160.80	Gamma (25, 0.155)	[67]
Cost of maintenance dose PPI	117.12	Gamma (25, 0.213)	[67]
Cost of *C. difficile*	5,837.32	Gamma (19.3, 0.003)	[9,39,40]

3 TreeAge Pro model structures

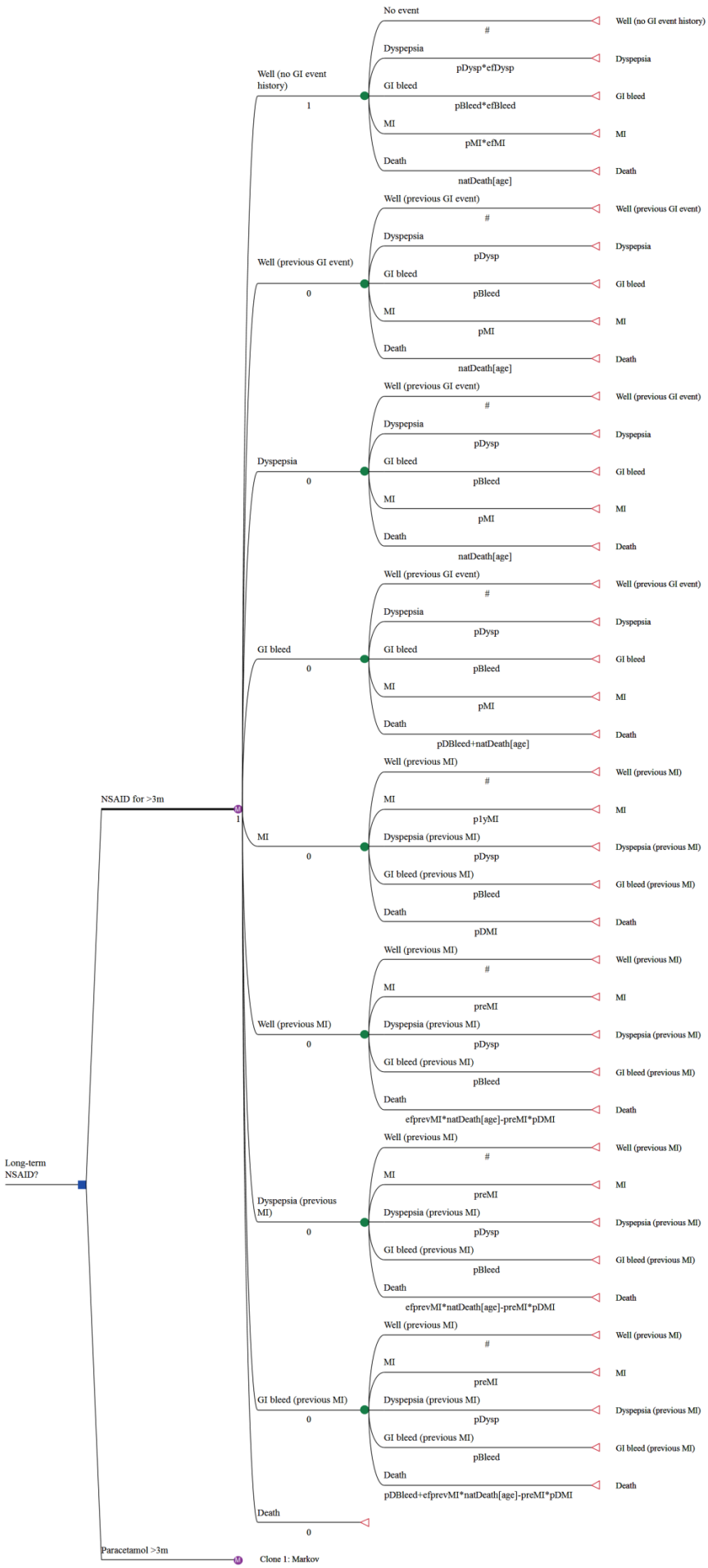

Figure A 2 Decision tree structure for NSAID Markov model in TreeAge Pro

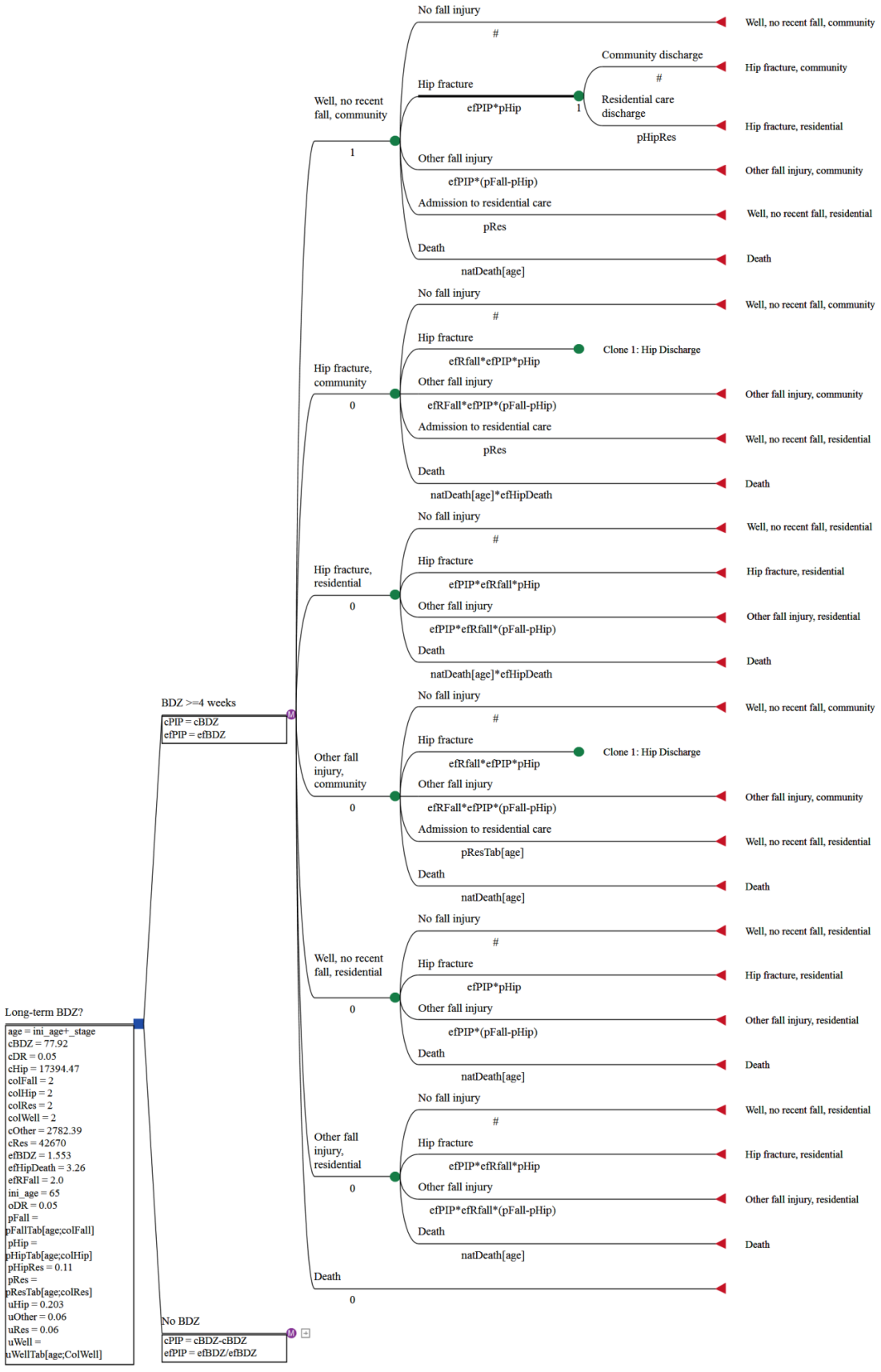

Figure A 3 Decision tree structure for benzodiazepine Markov model in TreeAge Pro

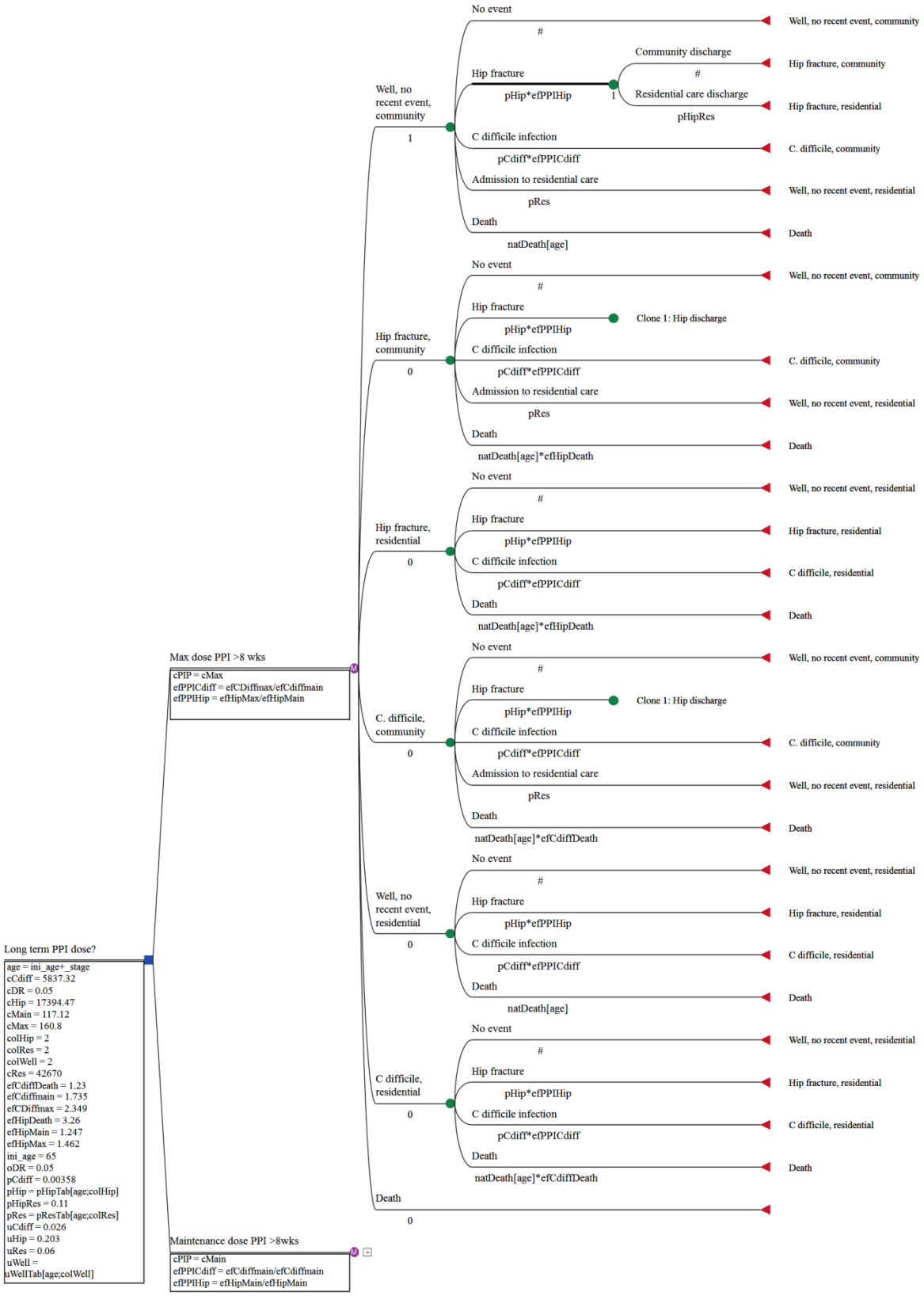

Figure A 4 Decision tree structure for PPI Markov model in TreeAge Pro

4 Probabilistic sensitivity analysis methods

Uncertainty associated with imprecision of the parameter inputs was incorporated into the model using probabilistic sensitivity analysis (PSA) to allow 95% credible intervals (CIs) to be fitted. A distribution of possible values for each parameter was specified, which were fitted under the assumption of a homogenous sample of patients informing parameter estimates (i.e. heterogeneity between patient sub-groups was not investigated). The distribution type used for each parameter reflected the form of data the parameter takes and the standard distributional assumptions used when estimating CIs (as detailed below).[38] The distributions fitted for each parameter were calculated from data available in published sources and these are reported in Table A 1. Each model was run over 10,000 iterations and a random value for each parameter input was sampled from the specified distribution for each run. The outputs of each iteration were recorded to provide a distribution of cost and effect differences and the 2.5th and 97.5th percentiles for these differences were used to estimate 95% CIs. Statistical significance was assumed if the 95% CI for the incremental costs and effects did not include zero. The outputs of each iteration were also plotted on a cost-effectiveness (CE) plane to compare the distribution of ICER estimates for each PIP.

4.1 Approaches used to specify distributions for parameters

4.1.1 Probability parameters

As probabilities can only range between zero and one, the distribution specified must adhere to this limit so that impossible values are not selected from the distribution. A beta distribution is suitable for binomial data as it is constrained between zero and one. It is characterised by two parameters, α and β. In a single study where the number of events and sample size are known, the value of α can be set to the number of events and β to the sample size minus the number of events to specify the beta distribution for uncertainty around the probability point estimate. In the absence of this information, for example if using findings from a meta-analysis, the distribution can be fitted by the method of moments if the mean or proportion and standard error or variance are given, using the following equations:

$$\alpha = \bar{\mu}\left(\frac{\bar{\mu}(1-\bar{\mu})}{s^2} - 1\right),$$

$$\beta = \alpha.\frac{(1-\bar{\mu})}{\bar{\mu}}.$$

4.1.2 Relative risk parameters

Relative risks (RR) are composed of ratios of ratios ranging from zero to infinity and the confidence intervals for which are calculated on the log scale. Therefore, the appropriate distribution for these parameters is lognormal and a distribution can be specified as N(ln[RR], se[ln(RR)]), by taking the natural log of the point estimate and calculating the standard error of this using reported Cis as follows:

$$se[\ln(RR)] = \frac{\ln(Upper\ CI) - \ln(Lower\ CI)}{2 \times 1.96}.$$

4.1.3 Cost parameters

Cost data is constrained to positive values so is generally truncated (to exclude negative values) and right-hand (or positively) skewed as there tends to be small numbers of cases with high costs on the right side of the distribution. Often Poisson or gamma distributions are used to represent cost data, although lognormal distributions can also be used. A gamma distribution can be fitted with the method of moments. For gamma(α,β), the mean ($\bar{\mu}$) is equal to αβ and the variance (s^2) is equal to $\alpha\beta^2$, which can be rearranged to:

$$\alpha = \frac{\bar{\mu}^2}{s^2},$$

$$\beta = \frac{s^2}{\bar{\mu}}.$$

4.1.4 Utility parameters

Utility parameters tend to fall within the range zero to one, however they can technically range into negative values, representing states worse than the reference 'worst health state' used to derive them (usually death). For utilities far from zero, a beta distribution can be used. Another approach is to use the disutility or utility decrement for a health state (1 – utility), which are constrained between zero and positive infinity and can be specified as gamma or lognormal distributions.

In this analysis, we used a beta distribution for the utility in the 'Well' state using the approach outlined in section 3.1.1, and gamma distributions for disutilities using the approach outlined in section 3.1.3.

5 Published estimates of intervention effectiveness

In the OPTI-SCRIPT trial of a complex intervention in general practice, the relative risk of being on a long-term maximal dose PPI post-intervention was 0.45 (i.e. a 55% reduction) compared to usual care.[68] For NSAIDs, a recent trial of education, informatics and incentives in general practice demonstrated a significant reduction of 49.8% in high-risk prescribing relating to NSAIDs and gastroprotection (i.e. a risk reduction of 0.498).[69] A trial to reduce inappropriate prescribing of benzodiazepines using direct patient education demonstrated an additional 23% of those in the intervention group had discontinued benzodiazepines compared to control (i.e. a risk reduction of 0.23).[70]

In the economic evaluation of potential interventions to reduce PIP, a new decision was framed between implementing an intervention to reduce PIP or usual care, as illustrated in Figure A 5 below for NSAIDs. The effectiveness estimate of the published interventions for each type of PIP was used as an input in each analysis as the proportion of patients receiving the intervention who are switched from the PIP drug to the more appropriate alternative.

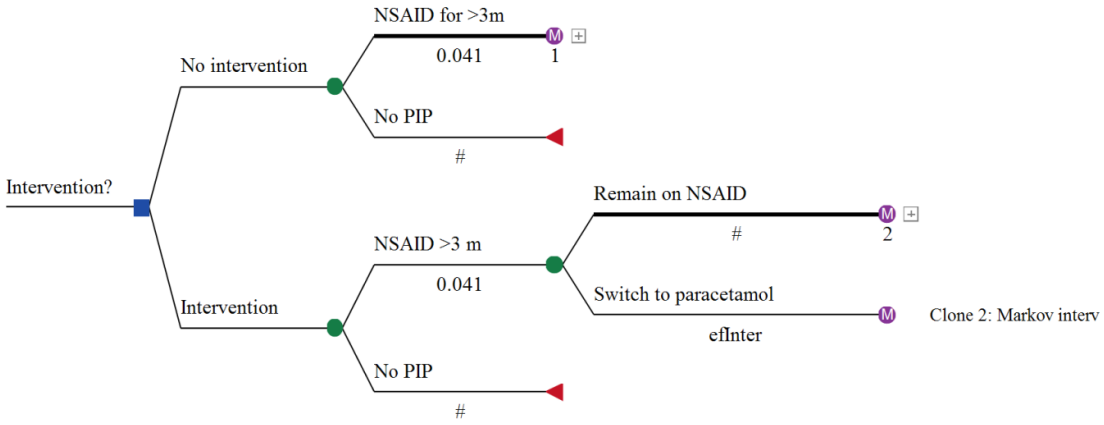

Figure A 5 Decision tree structure of published intervention analysis for NSAIDs

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Appendix 3 – Supplementary results of economic evaluation analysis

Base case analysis

Table A 2 Number of adverse events for PIP and non-PIP scenarios

Adverse events	PIP cases	Non-PIP cases	Difference	NNH
NSAID model				
GI bleeds	48	25	23	43
Dyspepsia	1141	973	168	6
MIs	213	172	41	25
Benzodiazepine model				
Hip fractures	296	184	113	9
Other injuries	1864	1159	704	1.4
PPI model				
Hip fractures	195	167	28	36
C. difficile infections	94	70	24	41
Adverse events	PIP cases per 1000 person years	Non-PIP cases per 1000 person years	Difference	NNH
NSAID model				
GI bleeds	60.34	50.91	9.44	106
Dyspepsia	2.54	1.30	1.24	804
MIs	11.24	9.00	2.24	447
Benzodiazepine model				
Hip fractures	15.22	9.44	5.78	173
Other injuries	95.74	59.56	36.18	28
PPI model				
Hip fractures	10.04	8.59	1.45	689
C. difficile infections	4.84	3.57	1.27	791

Abbreviations: NNH, number needed to harm; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; QALYs, quality-adjusted life years.

Probablistic sensitivity analysis

The outputs of each iteration of the probabilistic sensitivity analysis were plotted on a CE plane to compare the distribution of ICER estimates for each PIP. Figure A plots the outputs for each iteration using the alternative NSAID scenario where individuals taking NSAIDs remain on this medication following any adverse event as opposed to the base case analysis where individuals are switched to paracetamol following an adverse event. This scenario was more comparable to the PPI and benzodiazepine models where in the base case analysis it was assumed that individuals remained on therapy regardless of adverse events, due to unlikely attribution of the adverse events in the case of PPIs and dependence and withdrawal effects in the case of benzodiazepines.

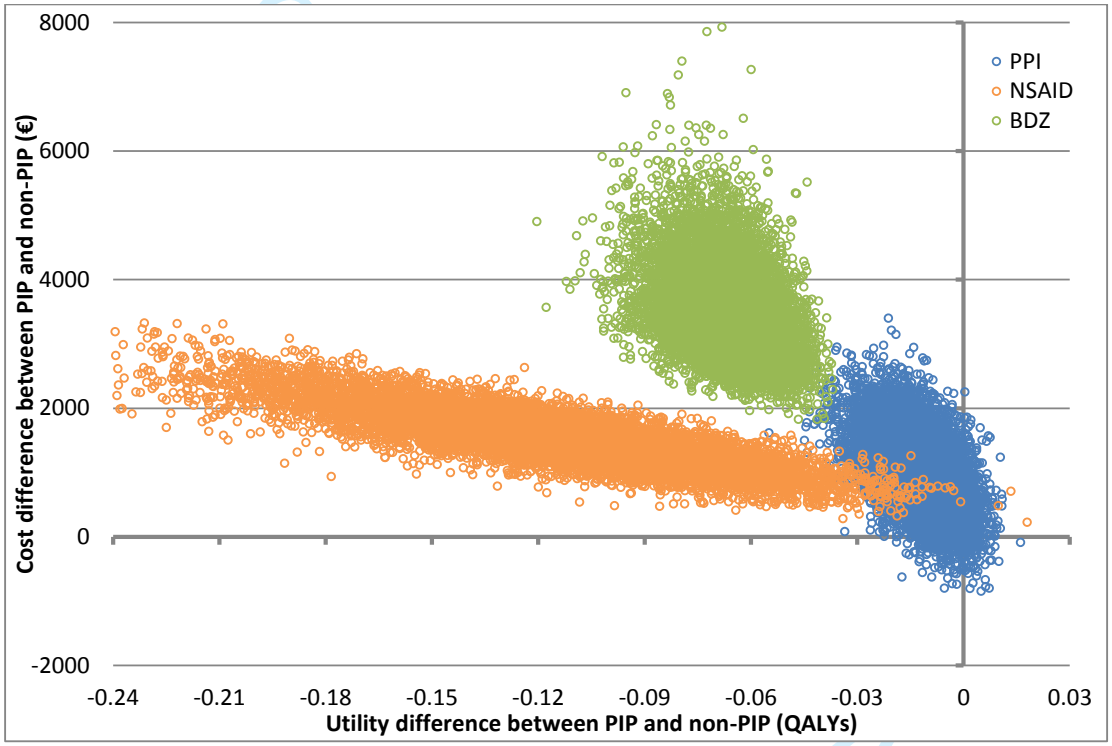

Figure A 6 Incremental costs and utilities for PIP compared to non-PIP from probabilistic sensitivity analysis using alternative NSAID scenario

Evaluation of cost-effectiveness of published interventions

The results of threshold analysis for an intervention to target NSAID prescribing are plotted in **Figure A** showing whether the intervention is preferred to no intervention at a cost-effectiveness threshold of €45,000 per QALY as intervention cost and effectiveness vary. The arrow shows how an intercept can be used to determine the cost at which the intervention becomes cost effective given a certain effectiveness, or vice versa. For example, at a €500 intervention cost, the intervention targeting NSAID prescribing would be cost effective if it reduces PIP by at least 12.6%.

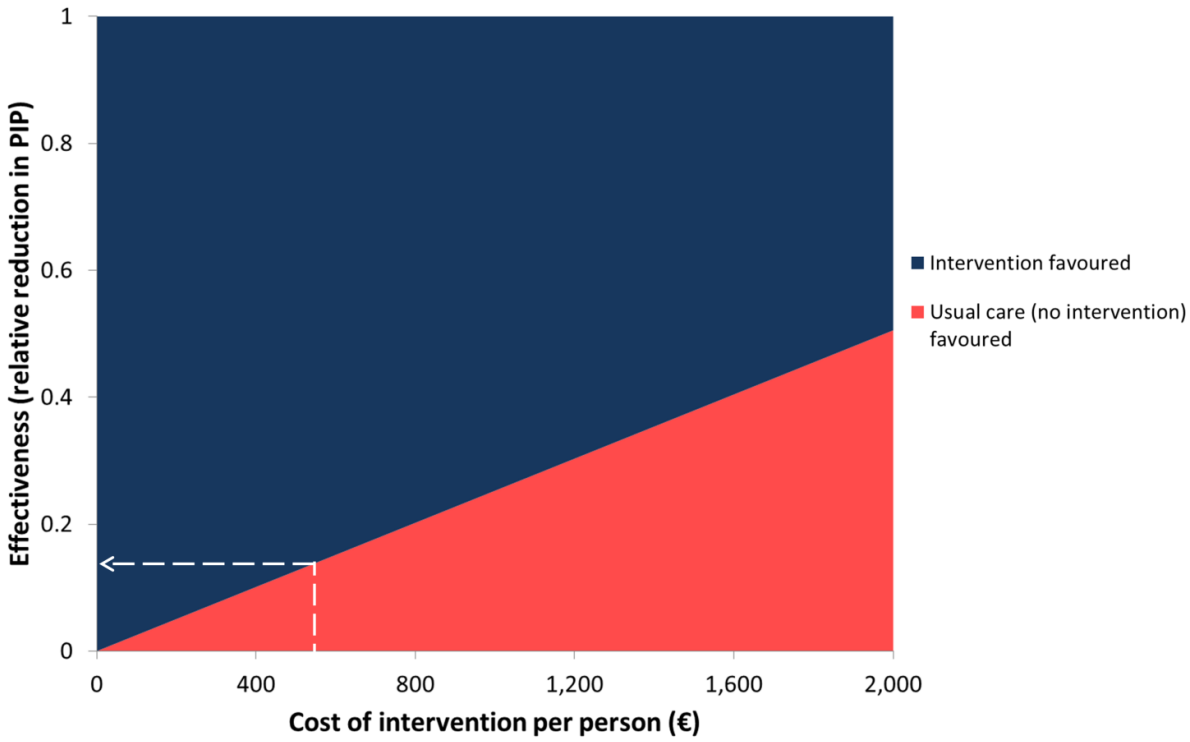

Figure A 7 Threshold effectiveness value for NSAID intervention at intervention cost of €500 and cost-effectiveness threshold of €45,000 per QALY

Section/item	Item No	Recommendation	Reported on page No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 4, paragraph 1
		Present the study question and its relevance for health policy or practice decisions.	Page 4, paragraphs 2-3
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 5, paragraph 1
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 5, paragraph 1
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 5, paragraph 1
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 5, paragraph 1 and Table 1
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5 paragraph 1
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 5, paragraph 1
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 5, paragraph 1 and Page 6, paragraphs 2-3
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Technical appendix, section 2.1
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Page 6, paragraph 2 and Technical appendix, section 2.3
Estimating resources and costs	13a	*Single study-based economic evaluation:*Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate	Page 6, paragraph 3 and Technical

		resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	appendix, section 2.2
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 6, paragraph 3
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 5, paragraph 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 6-7 (Assumptions) and Technical appendix, section 1
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 7-8 (analytical methods) and Technical appendix, section 3-5
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Technical appendix, Table A1 and Section 2
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 9, paragraph 1 and Table 2.
Characterising uncertainty	20a	*Single study-based economic evaluation:*Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 9, paragraph 1 and 2, Figure 1 and Figure A7
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			

Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 11-13
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 15
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 15

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Economic impact of potentially inappropriate prescribing and related adverse events in older people: a cost-utility analysis using Markov models

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Economic impact of potentially inappropriate prescribing and related adverse events in older people: a cost-utility analysis using Markov models

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Abstract

Objectives: To determine the economic impact of three drugs commonly involved in potentially inappropriate prescribing (PIP) in adults aged ≥65 years, including their adverse effects (AEs): long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, and proton pump inhibitors (PPIs) at maximal dose; to assess cost-effectiveness of potential interventions to reduce PIP of each drug.

Design: Cost-utility analysis. We developed Markov models incorporating the AEs of each PIP, populated with published estimates of probabilities, health system costs (in 2014 euro), and utilities.

Participants: A hypothetical cohort of 65 year olds analysed over 35 one-year cycles with discounting at 5% per year.

Outcome measures: Incremental cost, Quality-Adjusted Life Years (QALYs) and incremental cost-effectiveness ratios with 95% credible intervals (CIs, generated in probabilistic sensitivity analysis) between each PIP and an appropriate alternative strategy. Models were then used to evaluate the cost-effectiveness of potential interventions to reduce PIP for each of the three drug classes.

Results: All three PIP drugs and their AEs are associated with greater cost and fewer QALYs compared to alternatives. The largest reduction in QALYs and incremental cost was for benzodiazepines compared to no sedative medication (€3,470, 95%CI €2,434, €5,001; -0.07 QALYs, 95%CI -0.089, -0.047), followed by NSAIDs relative to paracetamol (€806, 95%CI €415, €1,346; -0.07 QALYs, 95%CI -0.131, -0.026), and maximal dose PPIs compared to maintenance dose PPIs (€989, 95%CI -€69, €2,127; -0.01 QALYs, 95%CI -0.029, 0.003). For interventions to reduce PIP, at a willingness-to-pay of €45,000 per QALY, targeting NSAIDs would be cost-effective up to the highest intervention cost per person of €1,971. For benzodiazepine and PPI interventions, the equivalent cost was €1,480 and €831 respectively.

Conclusions: Long-term benzodiazepine and NSAID prescribing are associated with significantly increased costs and reduced QALYs. Targeting inappropriate NSAID prescribing appears to be the most cost-effective PIP intervention.

Strengths and limitations of this study

- This study represents a novel application of economic modelling methods to assess three common types of potentially inappropriate prescribing.
- Analysis included the principal adverse effects of each potentially inappropriate medication.
- Uncertainty of estimates was quantified using probabilistic sensitivity analysis.
- The study did not consider differences in adverse event risk among individual drugs within each class, or heterogeneity in economic impact among patient sub-groups.

Introduction

Potentially inappropriate prescribing (PIP), the use of medicines where the risks outweigh the benefits, is prevalent among adults aged ≥65 years, particularly in individuals taking multiple medicines or with multiple chronic conditions.[1,2] Several explicit measures of PIP have been developed, including Beers criteria and the Screening Tool for Older Person's Prescriptions (STOPP), and while their relationship with some patient outcomes has been evaluated, the effect on the wider health system is also important to consider, in particular on healthcare costs.[3] The use of potentially inappropriate medicines can have an impact on health care costs due to pharmaceutical expenditure relating to the prescriptions themselves and due to managing the adverse events which may result. In two systematic reviews, one of studies assessing the STOPP criteria and another on the economic impact of inappropriate drug prescribing more generally, only direct medication costs of PIP drugs were assessed.[3,4] Increased life expectancy has called into question the use of 65 years and above as a threshold for old age, however the literature on PIP (including STOPP) still focuses on this population due to physiological changes in ageing and the prevalence of multiple co-morbidities which can predispose to medication harm.[3]

Furthermore, in only assessing the direct cost of inappropriate drugs, the economic consequences of appropriate prescriptions used as an alternative to PIP medicines are not accounted for.[4,5] The costs of managing any resulting adverse events have yet to be quantified for PIP as a whole, and have only been assessed for individual medication classes to date, such as benzodiazepines and NSAIDs.[6–8] The economic impact of PIP is important when considering whether interventions to reduce PIP are an efficient use of resources and health professionals' time relative to other competing priorities. Few economic evaluations of trials to optimise prescribing for older people have been published,[3,9,10] which may limit implementation of such interventions by decision-makers, given scarce healthcare resources.

A recent analysis of PIP among older adults in Ireland found that the most common indicators related to long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, and maximal dose proton pump inhibitors (PPIs).[2] NSAIDs are indicated for treating pain in arthritis and low back pain for example, however due to their gastrointestinal and cardiovascular risks, they are not recommended for long-term use. Benzodiazepines are sedative agents used to treat insomnia, but carry risks of day-time drowsiness as well as tolerance and dependence following long-term use. PPIs are used for gastrointestinal conditions such as peptic ulcer disease and gastro-oesophageal reflux disease. While maximal doses are indicated for up to 8 weeks in the majority of

cases, following this a maintenance dose has comparable efficacy if continued treatment is necessary. Despite strong evidence that the balance of benefits and harms for such prescriptions is unfavourable, the prevalence of these indicators ranged from 4% to 24% in a primary care population analysis (where most prescribing of these agents occurs).[2]

The aim of this study is to estimate and compare the economic impact of these three common indicators of PIP: long-term use of NSAIDs, benzodiazepines, and maximal dose PPIs. Specifically, we compare each of the three PIP drugs to a more appropriate treatment using Markov models to assess differences in quality and quantity of life and cost to the health system. We then apply the models to explore the cost-effectiveness of potential interventions based on recently published trials targeting these PIP drugs.

Methods

Markov models

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement was used in the design and reporting of this research (included as Appendix 1).[11] A Markov model was developed for each of the included PIP drugs using TreeAge Pro 2015 (TreeAge Software Inc., Williamstown, MA). This type of decision-analytic model was chosen to allow for time dependency, a particularly important consideration in the context of older people on long-term medicines.[12] The base case analysis used a target population of hypothetical 65 year olds who were community-dwelling in Ireland and had no current or previous adverse events relating to these PIP drugs. A health system perspective was used over a time horizon of 35 one-year cycles (i.e. to age 100) with a half cycle correction.[13] This perspective is recommended in national guidelines on economic evaluation,[14] and therefore only direct costs to the health system (including those relating to residential care) were considered. The primary decision maker is therefore Ireland's Health Service Executive which makes funding allocation decisions relating to health technologies. In each of the three cases, the PIP strategy was compared to an alternative strategy, selected as an appropriate therapeutic option instead of the PIP drug (with respect to effectiveness and safety). The models incorporated the principal adverse drug events relating to each PIP (see Table 1). The primary outcomes evaluated were costs and quality-adjusted life years (QALYs). Life years (LYs) and number/rate of adverse events were also quantified as secondary outcomes. A discount rate for costs, QALYs, and LYs was applied at 5% per annum, and was varied from 0% to 6% in sensitivity analysis, in line with guideline recommendations.[14]

This cohort consisted of healthy community-dwelling older people, therefore in each model, all individuals start in a 'Well' state (see Figure A1 in Appendix 2 for state transition diagrams for each model). In subsequent cycles, individuals could transition to other states as a result of adverse events relating to the potentially inappropriate medicines of interest. Individuals remain in the adverse event state for one cycle unless they have a further adverse event in the subsequent cycle, and otherwise they transition to the post-event state (if applicable) or the relevant 'Well' state. Mortality attributable to adverse events and background age-related mortality were included. An in-depth description of the structure and transitions for each model is included in section 1 of Appendix 2. The models were populated with parameter estimates (see Table A1) derived from published sources which are described in detail in section 2 of Appendix 2. As this study used only previously published data, there was no requirement for ethical approval or patient consent.

Model inputs

Transition probabilities

Probabilities of transitions between states for the three models were taken from published literature sources which reported rates or probabilities of the adverse events of interest. Population-based epidemiological studies with study samples representative of older community-dwelling adults were used, whenever possible, reflecting the baseline rate of adverse events for individuals in the appropriate alternative models (see Table A1). In the PIP models, a measure of the relative risk associated with the PIP drug was applied to the baseline probability for each adverse event. These were taken from meta-analyses of randomised controlled trials for NSAIDs,[15–17] meta-analyses of observational studies for benzodiazepines,[18,19] and for PPIs from a meta-analysis of observational studies,[20] and a single observational study.[21]. Annual probability of death from all causes was based on age-specific population rates for 2014 from the Central Statistics Office (CSO).[22] Excess mortality estimates following adverse events were taken from observational studies,[23–28] and were assumed to be independent of PIP exposure (i.e. the same post-event mortality was applied in both PIP and alternative scenarios).

Utility values

To increase comparability between the models, the same baseline utility value was applied to all 'Well' or no event health states. The source of these values were UK population norms for the EQ-5D visual analogue scale for people aged 65-74 and 75 years and over.[29] Utility decrements or disutilities, the annual reduction in utility due to an adverse event were taken from previous economic evaluations or studies that derived these values from patients with the relevant adverse event.[9,30–43] These were subtracted from this baseline utility to give the utility value for each state. Further details of these are provided in Appendix 2, section 2.

Costs

Each state was assigned a cost reflecting the average annual costs to the Irish health system for a patient in that health state, relating to hospital inpatient care, general practitioner, out-patient department, and emergency department visits, medicines, and long-term (residential) care. Costs in euro from 2014 were used, and, where not available, historical costs were inflated using the applicable Consumer Price Index Health sub index from the CSO. In the case of *C. difficile* infection, international estimates of attributable costs were inflated to 2014 costs using the CPI from the origin country, and were then converted to Irish costs using the Purchasing Power Parity index.[14]

Additional healthcare use attributable to adverse events was identified from published studies and Irish unit costs were assigned.[44]

Assumptions

It was assumed that prescribed medicines were consumed (i.e. full adherence) and over-the-counter use was not included in the models. Health states only related to the adverse events of each PIP, so it was assumed that there was no significant differences in efficacy between each PIP and the appropriate alternative, and no significant adverse effects of the appropriate alternative. In the NSAID model, following an adverse event, it was assumed that individuals would be switched to an appropriate alternative. In the other models, it was assumed that individuals remained on therapy regardless of adverse events, due to unlikely attribution of the adverse events in the case of PPIs and dependence and withdrawal effects in the case of benzodiazepines. The effect of this assumption was assessed in structural sensitivity analysis.

Analytic methods

Economic impact of PIP relative to appropriate alternatives

Model structures were assessed for face validity by the research team and models were cross-validated by comparison to other published models concerning these therapeutic areas.[45] Models were validated by double-programming in Microsoft Excel 2010 (Microsoft Corp., Redmond, WA) to detect structural or coding errors, and extreme value testing and comparison of cohort traces between TreeAge Pro and Excel were also conducted.[45] Only the base case analyses were programmed in Excel. The models programmed in Excel are available from https://doi.org/10.6084/m9.figshare.5818251.v1, and TreeAge Pro model structures are included as Figures A2-4 in section 3, Appendix 2.

Base case models were run for the PIP and appropriate scenarios using point estimates for transition probabilities, costs, and utilities (as shown in Table A1 in Appendix 2) and results are presented as mean differences in costs, QALYs, and LYs. An incremental cost-effectiveness ratio (ICER) was also calculated for each PIP, indicating the expected additional cost per additional QALY in the PIP scenario relative to the appropriate alternative scenario. Differences in the total number of adverse events for the PIP scenario compared to the appropriate scenario were also determined. Uncertainty associated with imprecision of the parameter inputs was incorporated into the model using probabilistic sensitivity analysis (PSA) to allow 95% credible intervals (CIs) to be fitted (see Appendix 2, section 4 for further details). The impact of varying specific parameter inputs, including

costs and discount rates, was assessed in one-way deterministic sensitivity analyses.[14] Although not pre-specified, we also considered treatment adherence in one-way sensitivity analysis. Up to 20% non-adherence was assessed, which applied a reduction to medication costs and a reduction in the proportion within each state who were exposed to the medication and the associated relative risk of adverse events.

Cost-effectiveness of potential interventions

In the second stage of the analysis, each model was used to evaluate the cost-effectiveness of a potential intervention to reduce prescribing of each PIP drug by switching patients to the more appropriate alternative. This analysis was in the form of a value of implementation analysis,[46] and a new decision was framed between implementing an intervention to reduce PIP or usual care, as illustrated for NSAIDs in Figure A5 in Appendix 2, section 5. The intervention was delivered once at the beginning of the model to all individuals on a long-term NSAID and resulted in a proportion of these people being switched to paracetamol for the duration of the model time horizon. The intervention cost per person and effectiveness (i.e. the relative reduction in the proportion on a long-term NSAID) were varied to determine circumstances in which the intervention would be preferred to no intervention at a willingness-to-pay or cost-effectiveness threshold of €45,000/QALY (the conventionally used threshold in Ireland),[14] as well as thresholds of €20,000/QALY and €0/QALY. These results were plotted and this was then repeated for benzodiazepine and PPIs. Threshold analysis was conducted using effectiveness estimates from recent primary care trials targeting these PIP drugs which have no published economic evaluation to date to determine maximal costs at which each medicines optimisation intervention would be cost-effective (see section 5 of Appendix 2 for a description of these trials).[47–49]

Patient involvement

Patients were not involved in the conception, design, or conduct of this research.

Results

Economic impact of PIP relative to appropriate alternatives

Based on the study parameters used (Table A1), for all three models the PIP scenarios were dominated by the appropriate treatment scenarios (i.e. they generated higher costs and fewer QALYs). The incremental costs and QALYs were largest in the benzodiazepine model, where being on the PIP drug generated an average of €3,470 higher costs and 0.07 fewer QALYs per patient compared to the appropriate alternative scenario (Table 2). For costs, this was followed by patients on a long-term maximal dose PPI relative to those on a maintenance dose and then being on long-term NSAIDs compared to paracetamol. The QALY loss in the NSAID model was 0.07 QALYs and 0.01 QALYs in the PPI model. The excess adverse events in the PIP scenarios relative to the appropriate alternative scenarios are shown in Table A2 (Appendix 3). Uncertainty in the outcomes is illustrated in Figure 1 showing the distribution of cost and QALY differences for each model in the PSA. The 95% CIs generated from the PSA showed incremental costs and QALY losses were statistically significant for the NSAID (95% CI €415to €1,346 costs; -0.131to -0.026 QALYs) and benzodiazepine models (95% CI €2,434to €5,001 costs; -0.089to -0.047 QALYs). For the PPI model, the difference in costs and QALYs between maximal dose and maintenance dose prescribing was not statistically significant (95% CI -€69to €2,127 costs; -0.029to 0.003 QALYs).

In one-way deterministic sensitivity analysis, the PIP scenario was still dominated by the appropriate alternative scenario in each model across the range of values for the investigated parameters and the rankings of the models by incremental costs and QALYs did not change (see Table 3). Similarly, the post-hoc sensitivity analysis of treatment non-adherence showed a reduction in both incremental costs and QALYs with increasing non-adherence. Altering the NSAID model structure to assume no switch from the PIP drug to paracetamol after an adverse event (i.e. if patients remained on a long-term NSAID regardless of adverse events occurrence, consistent with the benzodiazepine and PPI models) resulted in a larger cost difference (€1,494, 95% CI €756to €2,493) and QALY difference (-0.11 QALYs, 95% CI -0.042to -0.203) between the PIP and appropriate scenarios. The distribution of cost and QALY estimates under this assumption is plotted in Figure A6 in Appendix 3.

Cost-effectiveness of potential interventions

Applying these models to determine the cost-effectiveness of potential interventions, the relationship between intervention cost, effectiveness and preferred option (intervention or usual

care i.e. no intervention) is represented graphically for each PIP drug in Figure 2. Additionally, see Figure A7 in Appendix 3 for an example interpretation of these plots. Taking estimates of effectiveness from recently published trials targeting these PIP drugs,[47–49] an intervention which reduces potentially inappropriate NSAID use by 49.8% would be cost-effective up to a cost of €1,971 per person at a CE threshold of €45,000. For an intervention that resulted in 23% discontinuation among benzodiazepine users, the corresponding threshold cost would be €1,480 and for a 55% reduction in potentially inappropriate PPI use it would be €831 (Table 4). The rank order of these potential interventions depended on the CE threshold used. Taking the extreme case of a CE threshold of €0 per QALY (i.e. willing to pay nothing additional for any QALY gain), cost-effectiveness would be achieved for interventions targeting NSAIDs, benzodiazepines, and PPIs up to costs per patient of €401, €798, and €544 respectively (Table 4).

Discussion

For the three PIP Markov models considered, the costs were greater and there were fewer QALYs where the potentially inappropriate medicine was prescribed compared to an appropriate alternative strategy (Table 2). For PPIs, the differences between the PIP and appropriate alternative did not reach statistical significance due to uncertainty in the risk of adverse events attributable to using maximal doses relative to maintenance doses (Figure 1). Of the three PIP drugs considered in this study, benzodiazepines for greater than four weeks compared to no sedative medicine had the greatest cost and QALY impact per patient (Table 2). In the evaluation of the cost-effectiveness of reducing PIP of these drugs, targeting long-term NSAIDs prescribing would be most cost-effective due to the published effectiveness of the intervention that was evaluated, though the ranking depended on the CE threshold used (Table 4).

Context of the literature

No other studies appear to have assessed the economic impact of PIP defined by STOPP beyond direct costs of medicines.[3] Several studies have quantified the costs of adverse events relating to drug classes included in this analysis, although in different settings.[50] For NSAIDs, the costs associated with no gastroprotection among older patients with peptic ulcer disease in the UK, the excess costs of GI injury among older US Medicaid patients, and the comparative costs of harm due to different NSAIDs have been evaluated.[6,9,51] Benzodiazepine drug interactions, although not potentially inappropriate benzodiazepine prescribing, were associated with significantly increased healthcare costs in a regression analysis of older patients,[7] while a further case-control study considered the attributable fall-related hospitalisation costs.[52] They estimated the cost of fall-related hospitalisations attributable to benzodiazepines in the Netherlands as €48.5 million, which is 18.9% of the total cost of fall-related admissions. An economic modelling study comparing benzodiazepines to cognitive behavioural therapy or no treatment among older adults with insomnia considering a time horizon of only one year also found substantial falls-related costs associated with sedative drug use.[8] While decision-tree analysis has been used to evaluate different PPI treatment strategies, including dose reduction, to manage oesophagitis,[53] the economic impact of adverse events or inappropriate prescribing of PPIs has not been evaluated. Comparisons with the present study are difficult, as previous research has often presented results at the population level rather than the incremental cost per person over an extended time horizon.

Despite many studies of interventions to address appropriateness of prescribing in older people in primary care, but few economic evaluations have been published.[3,10] The PINCER intervention in

English GP practices was cost-effective in both the in-trial economic evaluation and the model-based cost-utility analysis over a 5-year time horizon beyond the trial.[9,54] However there was uncertainty in the model-based results due to a lack of precise estimates of harm in the published literature for some of the prescribing/monitoring errors targeted.[9] An older study of clinical pharmacist advice to older US veterans on five or more medicines and their doctors reported a cost of $7.50-30 (€12-48) per patient per unit improvement in the Medication Appropriateness Index.[55] Other published economic evaluations have focussed on appropriate prescribing of only specific drug classes, such as benzodiazepines,[56,57] psychiatric medicines,[58,59] or cardiovascular medicines.[60] Of all of these interventional studies, only the PINCER trial conducted a model-based economic evaluation presenting results as an ICER (i.e. cost per QALY). Several recent trials of primary care interventions have successfully reduced PIP drugs. The OPTI-SCRIPT intervention involved academic detailing by a pharmacist and a computer decision support system for GPs in Ireland and resulted in a reduction in PIP, and in particular in long-term use of PPIs at maximal dosage.[47] The Scottish DQIP intervention employing education, informatics and incentives to assist GPs reviewing older patients' prescribing effectively decreased high-risk prescribing of NSAIDs and other medicines, and reduced the rate of hospitalisation for GI bleeding and heart failure.[48] Finally, the EMPOWER trial demonstrated that a patient empowerment intervention delivered through Canadian community pharmacies results in greater discontinuation of benzodiazepines than standard care.[49] The cost-effectiveness of these interventions has yet to be demonstrated through published economic evaluations, and hence this study illustrates the use of Markov models to assess the cost-effectiveness of reducing PIP and the resulting adverse events.

Strengths and limitations

This is the first study to quantify the economic impact of PIP in older people, considering not just the medication cost but also the adverse consequences. The use of Markov models allowed for available evidence on harm relating to PIP criteria from the published literature to be combined. The analysis also incorporated uncertainty in these estimates and a number of model validation steps were conducted. This study directly compared three types of suboptimal prescribing with distinct adverse effects on a common scale of costs and QALYs. Similarly it illustrates that the cost-effectiveness of potential interventions to improve prescribing in older people can be assessed using Markov modelling to capture the long-term consequences of medicines optimisation.

This study has several limitations. Only the principal adverse effects of each PIP were included to reduce the complexity and increase transparency of the models. Similarly, although prevalent

among older adults, we did not consider drug-drug and drug-disease interactions or exacerbations of underlying conditions within the models. A number of model assumptions were applied to address this study's aim. Firstly, as the STOPP criteria refer to drug classes, we used pooled estimates for each class for the risk of adverse effects to provide the average economic impact of each PIP, and heterogeneity within drug classes was beyond the scope of this study. Similarly we did not consider strategies that modify risks, such as gastroprotection with NSAIDs to prevent GI adverse events with NSAIDs. Secondly the cohort under consideration were 65 year olds, assumed to be continuous users of each PIP, and in the intervention evaluation, the reduction in PIP was assumed to be sustained over the full time horizon. In reality, patients may spend some time exposed and unexposed, however, these assumptions allowed comparison of the overall effects of each PIP. We considered treatment adherence in sensitivity analysis and although adherence to these medication classes is likely to be high given their symptomatic effects, adherence be lower may in some cases than is considered here. The analyses was performed on a cohort basis to assess the average costs and effects, which does not reflect the variability of these outcomes among individuals, where some patients may incur large costs and have a greater reduction in QALYs. Heterogeneity was also not considered, as the research did not aim to evaluate how the economic impact may vary among patient subgroups. Further research should determine the extent to which differences in individual patient characteristics may alter the economic impact of PIP. This analysis focussed only on adverse effects of prescribing deemed to be potentially inappropriate, however appropriate alternative were selected on the basis of similar effectiveness and limited adverse effects. Although these types of prescribing are generally regarded as inappropriate for older adults, there may be circumstances where patients and their doctors weigh the benefits and harms and decide that the "inappropriate" prescription is optimal for them individually.

Implications for policy and practice

Trial-based economic evaluations may not always be informative for policy-maker decisions due to, for example, relevant comparators not being included, an insufficient time horizon, or measurement of intermediary endpoints (e.g. serum cholesterol) or process measures (e.g. PIP) rather than final outcomes.[44] Modelling approaches can overcome these weaknesses, by allowing all relevant evidence to be synthesised, incorporating alternative treatments not directly compared in a trial, and extrapolating beyond the duration of the trial to assess long-term outcomes.[12] Adoption of economic modelling approaches could increase the number of informative economic evaluations of prescribing safety interventions, such as in the PINCER trial.[9] Such methods may be

particularly useful in evaluating services to improve other aspects of medicines use where the benefits may not manifest during the period of a trial, for example, interventions to improve adherence to preventative medicines.[61] Future trials of new or expanded services should conduct robust economic evaluations and include long-term consequences to inform policy-makers' decisions on implementation and funding allocation. Cost-utility analyses presenting results as cost per QALY are most informative, allowing policy-makers to compare interventions and make funding decisions across therapeutic domains. Model-based approaches, as illustrated here, are an effective method to produce these estimates and evaluate interventions which affect outcomes across physiological systems.

Prescribing of potentially inappropriate medicines has significant economic implications, and interventions to reduce PIP are likely to be cost-effective if implemented into primary care for older people. The 95% CIs for cost and QALY differences in the PPI model both included zero, which, similar to the PINCER trial, was due to uncertainty relating to the adverse effects.[9] This indicates that more information is needed on the safety of maximal compared to maintenance doses,[62] and therefore these results should not deter efforts to deprescribe PPIs where their use is potentially inappropriate.[2,47] As illustrated in Table 4, the CE threshold being used by policy-makers (i.e. the cost they are willing to pay for a QALY) can influence which interventions are funded. Placing a greater monetary value on each QALY will favour interventions that improve quality and quantity of life over those that reduce healthcare costs. While an explicit CE threshold exists for new drugs in the Irish health system, it is less clear whether the same applies to other interventions, such as those to improve prescribing.[63] It may be that a lower CE threshold applies to these, for instance, if no additional funding is available for medicines optimisation services and only cost-saving interventions are acceptable to decision-makers. Using a different CE threshold may alter healthcare decisions and potentially result in less net benefit for patients across the health system.[63]

Conclusions

Potentially inappropriate prescribing of benzodiazepines and NSAIDs carry a statistically significant cost, to both the health system and patients, and there is an economic case for implementing effective interventions to improve prescribing of these medications for older people. Maximal dose PPI use is highly prevalent but evidence of harms is less certain, and so further studies should consider whether continuing maximal dose PPI is associated with increased risks compared to maintenance dose prescribing in order to establish whether targeting this is an efficient use of

resources. Future research should also evaluate which patient subgroups inappropriate medication use have the greatest economic impact on, and thus, which patients would most benefit from prescribing optimisation interventions to maximise cost-effectiveness.

Data sharing: Markov models coded in Microsoft Excel are available at https://doi.org/10.6084/m9.figshare.5818251.v1 and data inputs are included in the technical appendix (Table A1, Appendix 2).

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Transparency statement: FM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Figures

Figure 1 Incremental costs and utilities for PIP compared to appropriate from probabilistic sensitivity analysis for each model (northwest quadrant)

Figure 2 Cost and effectiveness at which interventions would be cost-effective at a cost-effectiveness threshold of €45,000 per QALY for a) benzodiazepine, b) PPI, and c) NSAID models

Tables

Table 1 Description of included criteria from the Screening Tool for Older Persons' Prescriptions (STOPP)

Potentially inappropriate prescription	Comparator	Prevalence [2]	Adverse events represented
NSAID >3 months	Paracetamol	4.1%	Dyspepsia Gastrointestinal bleed Myocardial infarction
Benzodiazepine >4 weeks	No sedative medication	4.3%	Hip fracture Other fall injuries
PPI maximal dose >8 weeks	Maintenance dose PPI	23.6%	Hip fracture *Clostridium difficile* infection

Table 2 Cost, effect, and ICER outputs for PIP compared to appropriate scenarios for each model

Strategy	Cost, €	Incr. Cost, € (95% CI)	QALYs	Incr. QALYs (95% CI)	ICER, €/QALY	LYs	Incr. LYs
NSAID model							
Paracetamol >3m	2,603		8.72			11.54	
NSAID for >3m	3,409	806 (415 to 1,346)	8.65	-0.07 (-0.131 to -0.026)	-11,511	11.46	-0.08
Benzodiazepine model							
No benzodiazepine	25,158		8.78			11.69	
Benzodiazepine ≥4 wks	28,628	3,470 (2434 to 5001)	8.72	-0.07 (-0.089 to -0.047)	-52,672	11.65	-0.04
PPI model							
Maintenance dose >8 wks	24,831		8.82			11.70	
Maximal dose >8 wks	25,819	989 (-69 to 2127)	8.81	-0.01 (-0.029 to 0.003)	-85,279	11.68	-0.02

Abbreviations: CI, credible interval; ICER, incremental cost-effectiveness ratio; LYs, life years; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; QALYs, quality-adjusted life years.

Table 3 One way deterministic sensitivity analysis results

	NSAID model	Benzodiazepine model	PPI model
	Incremental effect (QALYs)		
Outcome discount rate			
0	-0.157	-0.175	-0.035
0.02	-0.111	-0.115	-0.022
0.04	-0.082	-0.079	-0.014
0.06	-0.061	-0.056	-0.010
Non-adherence to treatment			
10%	-0.064	-0.059	-0.011
20%	-0.058	-0.052	-0.010
	Incremental cost (€)		
Costs discount rate			
0	1,145.45	6,497.62	1,767.79
0.02	984.56	4,978.65	1,379.78
0.04	858.79	3,893.76	1,099.22
0.06	758.79	3,108.09	893.40
Inpatient cost of *C. difficile*			
€4,000.00	-	-	961.63
€6,398.72	-	-	996.79
€8,797.45	-	-	1,031.94
€11,196.17	-	-	1,067.09
PIP drug cost[a]			
Low	349.20	3,016.20	478.15
High	1,125.73	4,474.65	2,166.44
Non-PIP drug cost[b]			
Low	1,192.38	-	1,673.52
High	660.57	-	477.64
Non-adherence to treatment			
10%	740.56	3,117.12	900.42
20%	672.11	2,765.54	810.45

[a] PIP drug cost range (€) NSAID: 74.82-202.00, benzodiazepine: 38.96-164.16, PPI: 117.12-261.60.

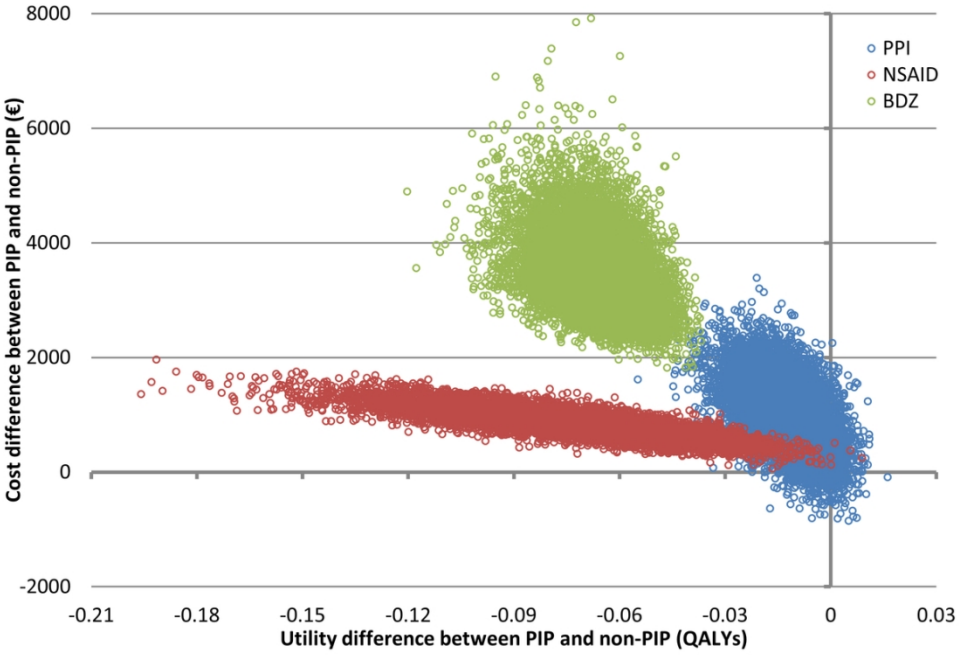
[b] Non-PIP drug cost range (€) NSAID: 38.40-120.00, PPI: 56.56-160.80.

Table 4 Threshold values across cost-effectiveness thresholds for intervention cost at levels of effectiveness from published trials

	NSAIDs	**Benzodiazepines**	**PPIs**
Intervention effectiveness (risk reduction)[a]	0.498	0.23	0.55
	Threshold cost (€) at published intervention effectiveness[a]		
WTP (€ per QALY)			
0	401	798	544
20,000	1099	1101	671
45,000	1971	1480	831

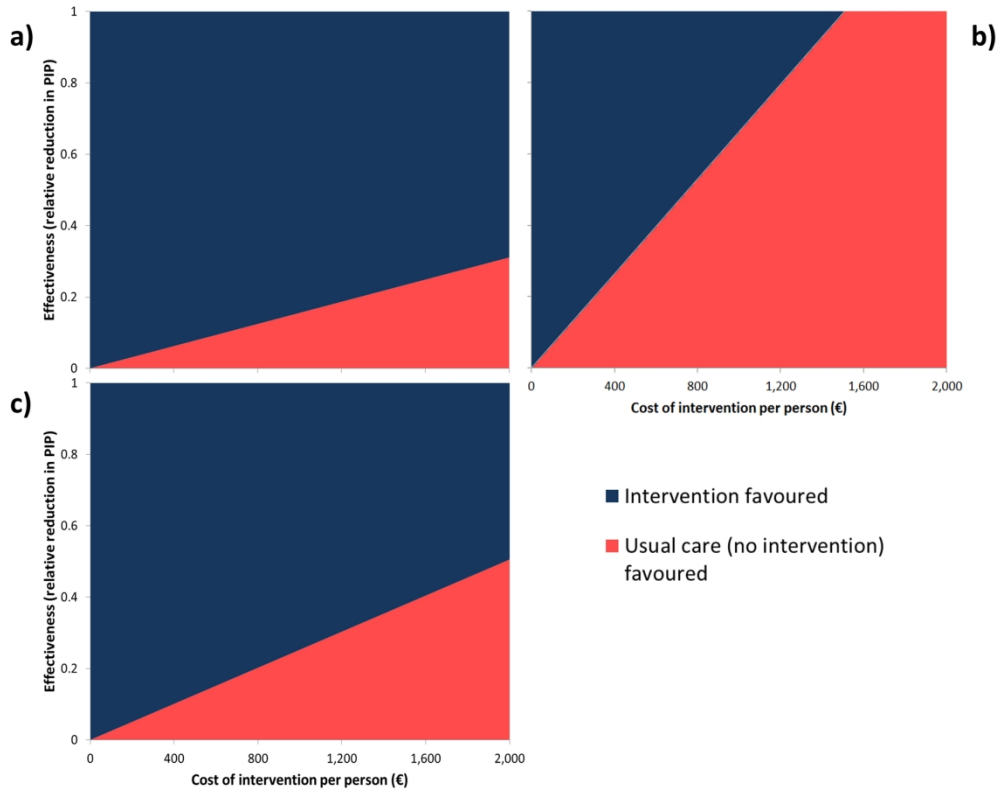
Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; QALY, quality-adjusted life year; WTP, willingness-to-pay.

[a] Effectiveness estimates used were taken from Dreishulte et al. for NSAIDs,[48] Tannenbaum et al. for benzodiazepines,[49] and Clyne at al. for PPIs.[47]



Incremental costs and utilities for PIP compared to appropriate from probabilistic sensitivity analysis for each model (northwest quadrant)

106x71mm (300 x 300 DPI)



Cost and effectiveness at which interventions would be cost-effective at a cost-effectiveness threshold of €45,000 per QALY for a) benzodiazepine, b) PPI, and c) NSAID models

166x132mm (300 x 300 DPI)

Appendix 1 – CHEERS checklist

Section/item	Item No	Recommendation	Reported on page No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 4, paragraph 1
		Present the study question and its relevance for health policy or practice decisions.	Page 4, paragraphs 2-3
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 5, paragraph 1
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 5, paragraph 1
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 5, paragraph 1
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 5, paragraph 1 and Table 1
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5 paragraph 1
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 5, paragraph 1
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 5, paragraph 1 and Page 6, paragraphs 2-3
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Technical appendix, section 2.1
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Page 6, paragraph 2 and Technical appendix, section 2.3
Estimating resources and costs	13a	*Single study-based economic evaluation:*Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	

	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 6, paragraph 3 and Technical appendix, section 2.2
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 6, paragraph 3
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 5, paragraph 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 6-7 (Assumptions) and Technical appendix, section 1
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 7-8 (analytical methods) and Technical appendix, section 3-5
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Technical appendix, Table A1 and Section 2
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 9, paragraph 1 and Table 2.
Characterising uncertainty	20a	*Single study-based economic evaluation:*Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 9, paragraph 1 and 2, Figure 1 and Figure A7
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not	N/A

		reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 11-13
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 15
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 15

Appendix 2 - Technical Appendix

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1 Description of model structures and states

The states included in each model capture the possible consequences for a patient with a potentiall inappropriate prescription (PIP) and the typical resource use and increased risks following an event are described. The same model structures were used for both the PIP and non-PIP scenarios, with the only differences being transition probabilities and cost of the PIP or non-PIP treatment.

1.1 NSAID model

All patients start in the 'Well (no previous event)' state and remain here until they have a gastrointestinal (GI) event (dyspepsia or GI bleed), a myocardial infarction (MI), or die (top, Figure A 1). Patients are on diclofenac 75mg twice daily in the PIP arm or paracetamol 1,000mg four times daily in the non-PIP arm. In the non-PIP arm, the transition probabilities reflect the rates of the adverse events in the general non-steroidal anti-inflammatory drug (NSAID) non-user population, and in the PIP arm, the relative risk in NSAID users was applied to these probabilities.

Patients can transition to the 'Dyspepsia' state where individuals have persistent dyspepsia causing GI discomfort requiring consultation with a doctor and so they attend their general practitioner (GP) for an extra visit, are switched from diclofenac to paracetamol and receive a prescription for a proton pump inhibitor (lansoprazole 15mg once daily for four weeks). They return to the baseline (non-PIP) risk of further dyspepsia and if no further event occurs in the following cycle, they transition to the 'Well, GI event history' state.

Patients who transition to the 'GI bleed' state in this state attend the emergency department (ED), are admitted to hospital for investigation and management of upper GI bleeding, are switched from diclofenac to paracetamol and receive a prescription for lansoprazole 15mg once daily for four weeks. After discharge, they are expected to have additional healthcare use as a result of their GI bleed, namely two GP visits and two outpatient department (OPD) visits.[1,2] As with dyspepsia, they return to baseline risk of a further GI bleed and transition to the 'Well, GI event history' state if they have no further event in the following cycle. In the 'Well, GI event history' state, patients' therapy has been switched from diclofenac to paracetamol, so the cost of medication (paracetamol) and transition probabilities for further GI events or an MI from this state is equal in both the PIP and non-PIP arms.

Patients transition to the 'MI' state following an MI and remain here for one cycle unless they have a further MI in the following cycle. Patients who have an MI incur inpatient treatment costs, are switched from diclofenac to paracetamol and commence medications for secondary cardiovascular prevention. They also have an additional 11 OPD visits and attend their GP an extra 8 times in the

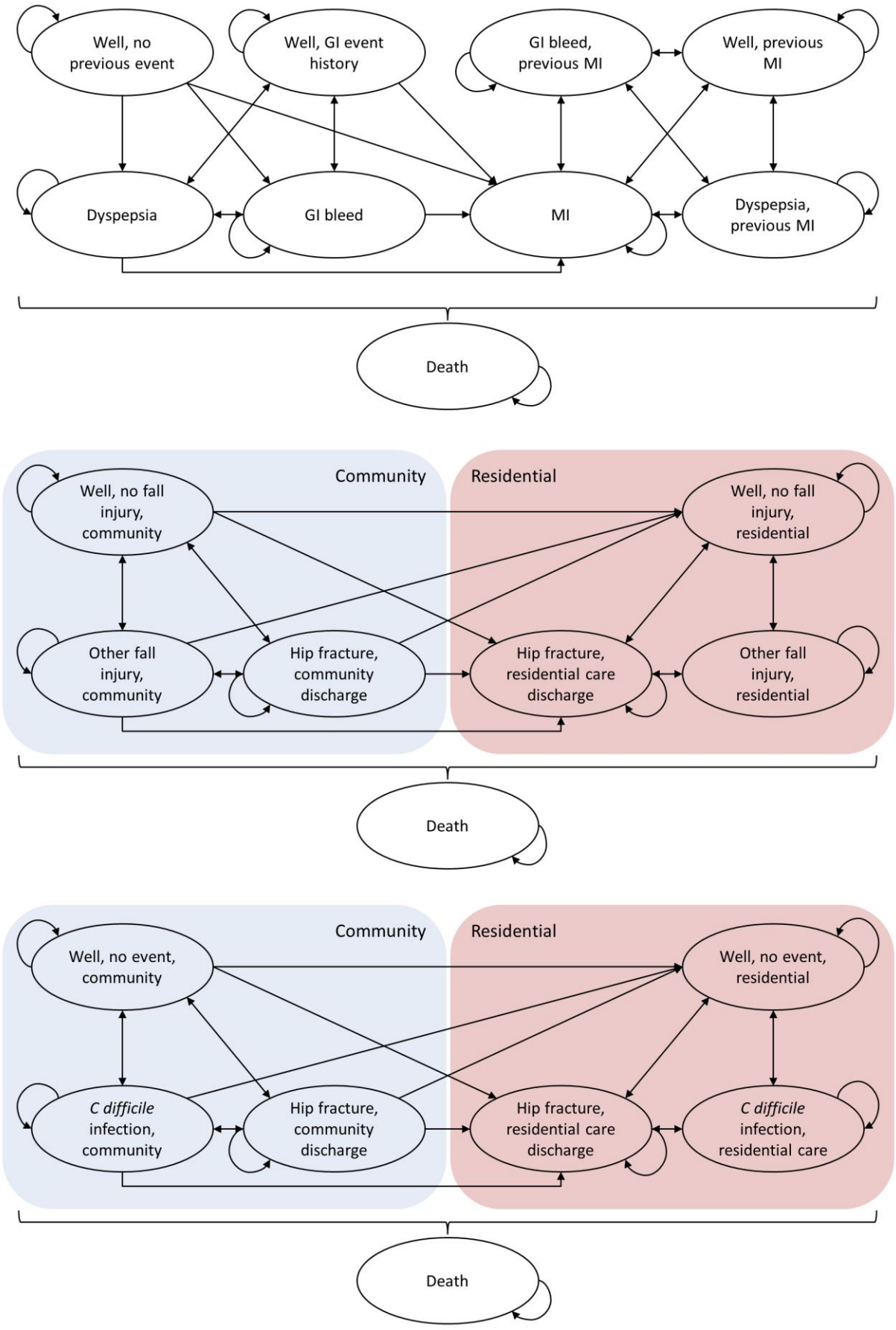

Figure A 1 Structures for NSAID (top), benzodiazepine (middle), and PPI (bottom) Markov models

year of an MI.[3] During this year patients are also at increased risk of a further MI.[4] If no event occurs in the subsequent cycle then patients transition to the 'Well, previous MI' state, where the probability of a subsequent MI falls, although it remains higher than in patients with no previous MI.[4] Patients in any 'previous MI' state incur the costs of attending two extra OPD appointments and two GP appointments per year,[3] as well as the cost of secondary preventive medicines and paracetamol.

1.2 Benzodiazepine model

All patients start in the 'Well, no fall injury, community' state as the cohort is community-dwelling and are assumed to have had no fall injury in the previous 12 months (middle, Figure A 1). The only cost incurred by patients in this state is the cost of the PIP medication, diazepam 5mg twice daily in the PIP arm, whereas no pharmacotherapy is prescribed in the non-PIP arm. Patients in the PIP arm remain on this medication with its associated cost and increased adverse events risk throughout the model i.e. no therapy switch occurs after an adverse event. From this state, a transition can occur following a hip fracture or some other fall injury that a patient seeks healthcare for. Hip fractures were divided into (i) those where the patient returns home and (ii) those which result in the patient being permanently admitted to a nursing home setting. Other events that can occur independently of falls are death and admission to a nursing home.

On having a hip fracture, patients transition to one of the two hip fracture states, depending on where they are discharged to following this event and remain here for one cycle, unless they suffer a further hip fracture. All hip fracture patients present at an ED, are admitted as inpatients and are discharged either back to the community or to a residential care setting. After discharge, hip fracture patients attend an average of 9 additional OPD appointments and have an excess of 10 visits to their GP.[5] For those discharged to the residential setting, there is the additional cost of nursing home residence. For 12 months following a hip fracture patients are at an increased risk of a further fall due to their recent injurious fall.[6] If they have no hip fracture or other fall injury in the following cycle, they transition back to the 'Well, no fall injury' state (either community or residential) and return to baseline fall risk.

All patients with a fall injury requiring healthcare that is not a hip fracture (such as bruising, soft tissue injuries or other types of fractures) transition to the 'Other fall injury' state. The costs incurred in this state are based on a weighted average of the prevalence of different injury types and typical healthcare use taken from an Irish costing study.[7] Half of patients with other falls injuries have one additional visit to their GP, 22% attend an ED, are not admitted and are referred

to their GP for a follow-up visit. Twenty percent attend ED with a non-hip fracture, are admitted as inpatients, and are discharged to community where they have 9 additional OPD visits and 6 extra GP visits.[5] The remaining 8% attend ED with other fall injuries, are admitted as inpatients and following discharge, are referred for one OPD visit and one GP visit for follow-up.[8] The only difference between community and nursing home setting is the additional cost of nursing home residence. As with the hip fracture states, patients remain in this state for one cycle unless they suffer another fall injury and are at an increased risk of a further fall while in this state.

Patients from all of the community-based states transition to the 'Well, no fall injury, residential' state based on the annual probability of being admitted to a nursing home. This background probability of nursing home admission is included as otherwise the number of admissions attributed to hip fracture in benzodiazepine users would be overestimated. Patients also transition to this state in the cycle following a hip fracture which results in permanent nursing home admission, or if they are nursing home residents who suffer a hip fracture or other fall injury. As only permanent admissions are represented in this model, no transitions occur from residential states back to community states.

1.3 PPI model

The model structure (bottom, Figure A 1) is similar to the benzodiazepine model. All individuals start in the 'Well, no event, community' where the only resource use is cost of the PIP or non-PIP medication (i.e. maximal dose proton pump inhibitor (PPI) or maintenance dose PPI). Patients in each arm remain on these medications, with their associated costs and increased adverse events risk, throughout the model i.e. no therapy switch occurs after an adverse event. A number of events can then occur, those that are affected by PIP exposure (*Clostridium difficile* infection and hip fracture) and those that are unaffected (death and admission to a nursing home). Similarly, following a transition to a residential state, patients remain there and no transition back to community can occur.

Following a hip fracture, patients transition to one of the 'Hip fracture' states (again depending on the setting they are discharged to) and remain in this event state for one cycle, unless they suffer a further hip fracture. Regarding healthcare utilisation, the same pattern that applied to this state in the benzodiazepine model was used here, including the additional cost of nursing home care for residential states.

Patients who develop *C. difficile infection* transition to the '*C difficile* infection' state for one cycle where the healthcare resource use is the cost of inpatient management attributable to the

infection, as community-dwelling patients aged 65 years or over are likely to be admitted as a result of an infection.[9] No further healthcare costs are incurred, and there is no increased risk of recurrence following a case (as recurrent cases were included in the baseline probability used) or being in a residential setting.

2 Sources of model inputs

The parameter inputs used in each model, along with the sources for these and the distributions used in the probabilistic sensitivity analysis are provided in Table A 1. The sources of each input are described in more detail below.

2.1 Transition probabilities

2.1.1 NSAID model

The probability of dyspepsia for non-NSAID users and the relative risk associated with NSAID use were taken from a meta-regression of trials and large exposure observational studies.[10,11] In these studies, a hypothesis was stated a priori that the prevalence in trial placebo groups would be lower than in the general population due to a selection bias in trials enrolling healthier patients. Therefore the probability was obtained by applying the relative risk to the prevalence from included NSAID versus NSAID trials. For GI bleeds, a pooled incidence rate in people aged 65 years and over from a review of epidemiological studies was used to calculate the probability.[12] Higher estimates have been reported, however these sources included NSAID users in the study populations. The risk of GI bleeds associated with naproxen and other NSAIDs was taken from a meta-analysis of randomised controlled trials.[13] The same risk of death following a GI bleed was applied to NSAID users and non-users,[14] and a UK hospital based study was the source of age-specific excess mortality estimates.[15] The baseline probability of an MI was estimated from an observational study of NSAID non-users aged 65 years and over and applied to all states with no previous MI,[16] and the probability of a further MI in the 12 months after an event was taken from a recent English population-based study.[4] This study was also the source for the probability of a subsequent MI more than one year post-MI which was applied to the previous MI states.[4] The pooled relative risk of MI on NSAIDs in the PIP arm was taken from the same meta-analysis of trials which yielded the effect on GI bleeds.[13] Probability of death in the year following an MI was taken from a study which provided the cumulative in-hospital and post-discharge mortality rate in a French cohort.[17] The long-term increase in relative mortality post MI was taken from a population-based study and applied to background mortality rate.[4] As this incorporated deaths from further MIs, the mortality from re-infarction was subtracted from this.

The increased risk of dyspepsia, GI bleeds, and MI in the PIP arm only applied to patients in the Well, no previous event state as any transition from this state following an event resulted in a switch from an NSAID to paracetamol. This switch from PIP to the non-PIP option after an adverse event was only applied to the NSAID model, not the benzodiazepine or PPI models. In the former

case patients/doctors may be reluctant to stop the benzodiazepine or it may be felt that stopping would pose a greater risk than continuing in older patients,[18] and for the latter a causal link between PPI exposure and adverse events is unlikely to be made.[19] The impact of relaxing this structural assumption for the NSAID model was assessed in sensitivity analysis.

2.1.2 Benzodiazepine model

This model only concerns falls which result in costs to the health service, therefore falls which result in no injury or falls injury which people do not seek healthcare for were excluded. The probability of a hip fracture was taken from a study reporting number of cases by age group from Irish hospital inpatient data.[7] This source was used in preference to another based on Irish data which provided similar estimates but which were presented separately by sex.[20] The estimate of the proportion of patients who are permanently admitted to a nursing home following hip fracture was taken from a cohort study in Northern Ireland which followed up patients one year post-fracture.[21] For the probability of other fall injuries, the probability of hip fracture was subtracted from the age-specific probability of an injurious fall.[22–25] The same probabilities for hip fracture and other fall injuries were applied to community and residential states. As no trials or meta-analysis of trials have been powered to detect the effect of benzodiazepines on falls, the estimate from the most recent meta-analysis of observational studies was used,[26] and two further meta-analyses had similar results.[27,28] An increased risk of a fracture or other fall injury was applied in the 12 months following a fracture or fall and this effect was taken from a meta-analysis of observational studies which reported the relative risk of a fracture in the year following a fracture.[6] The only attributable mortality included in this model was due to hip fracture,[29,30] and the relative hazard of mortality one year post fracture from a meta-analysis was applied to the all-cause mortality rate.[31] Background age-specific probability of nursing home admission (independent of hip fracture) was calculated from Irish data on the prevalence of nursing home residence.[32]

2.1.3 Proton pump inhibitors model

The probability of hip fracture, the joint probability of being admitted to a nursing home in the 12 months following a hip fracture, the relative mortality hazard in the 12 months following hip fracture, and the probability of admittance to a nursing home independent of hip fracture were taken from the same sources as the benzodiazepine model. The probability of *C. difficile* infection was based on the Irish national clinical guidance which reports the incidence in 2013.[9] The adjusted hazard ratio for mortality following *C. difficile* infection was taken from a propensity score matched-pairs analysis.[33] The source used for the increased risk of hip fracture in the PIP arm

relative to the non-PIP arm was a systematic review and meta-analysis of observational studies,[34] while the dose effects of PPIs on *C. difficile* infection was taken from a single observational study which reported this.[35] The inputs used were the risks in maximal dose PPI users relative to non-users divided by the risks in maintenance dose users relative to PPI non-users. For both fractures and *C. difficile*, there was no evidence of a significant difference between maximal dose and maintenance dose PPI users as reflected by overlapping confidence intervals, and in the case of hip fracture, the Cochran Q test for non-combinability. While this could not be accounted for in the point estimate, this was incorporated into the probabilistic sensitivity analysis when distributions were specified for these estimates.

2.2 Costs

The inpatient cost for managing a GI bleed was taken from the Health Service Executive (HSE) National Casemix Programme Ready Reckoner report which provides the average cost per case for various DRGs for 39 national hospitals participating in the National Casemix Programme.[36] This was consistent with the findings of an Irish study of patients admitted from a hospital ED with low-risk non variceal GI bleeding.[37] A study conducted in a large Irish hospital used a micro-costing approach was the source for the inpatient costs of a myocardial infarction.[38] Inpatient costs for hip fracture were taken from a previous economic evaluation which reported Irish cost data,[20] while for other fall injuries, the cost input was an average of the resource use weighted by the prevalence of different types of injuries, using Irish hospital costs for inpatient stays.[7] No Irish inpatient data was available on costs of *C. difficile* infection however a European systematic review provided several estimates, of which costs from a Northern Irish study were used and the impact of using other estimates from this review were examined in sensitivity analysis.[39,40]

For other healthcare utilisation, the typical excess number of OPD and GP visits post-discharge were taken from published case-control studies for GI bleeds,[1,2] MI (both in the first and in subsequent years post-event), [3] hip and other fractures,[5] and other non-fracture fall injuries.[8] The average cost of an OPD visit was taken from the HSE National Casemix Programme,[36] and cost per GP visit was calculated based on the average annual payment by the health service to GPs per General Medical Services (GMS) patient and the mean number of visits per patient.[41,42] The cost of attending an ED used was the average reported by the National Casemix Programme.[36] Medication costs were calculated using 2014 data from the HSE Primary Care Reimbursement Service (HSE-PCRS) for ingredient costs and a pharmacist dispensing fee of €5 was added for each month's supply to reflect the cost to the health service. As each PIP indicator refers to a drug class,

the medication most frequently prescribed in cases of PIP in a recent Irish population study was used i.e. diclofenac, diazepam and lansoprazole for NSAIDs, benzodiazepines and PPIs respectively.[43] The cost of one year's supply of one defined daily dose (DDD) per day was used. The costs of these PIP and non-PIP medications were varied in one-way sensitivity analyses over the range of costs of different drug molecules. In probabilistic sensitivity analysis, higher variance was included in the distributions for PPI costs as these are subject to continued price reductions through reference pricing.[44] The cost of secondary preventive medications (aspirin 75mg, atenolol 50mg, ramipril 5mg, and simvastatin 20mg) was included for the MI and post-MI states. The annual cost to the health service for a person in nursing home residence was determined from 2014 data on HSE spending on the Nursing Home Support Scheme and the number of individuals funded through this.[45]

2.3 Utilities

The preferences used in weighting for QALYs can be directly measured using rating scale, standard gamble or time trade off (TTO) methods. As these methods can be time-consuming and complex to use, an alternative is multi-attribute utility systems such as the EQ-5D-3L. Firstly, patients describe the health state they are in using a generic descriptive system of attributes which captures all important dimensions of the state. Secondly, valuations for each of these attributes derived from the general public are combined to determine an overall quality for the health state. In the EQ-5D-3L, five attributes are included (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and for each of these three response levels are defined. A valuation or tariff is estimated for all possible health states (3^5 = 243) by a large sample of individuals valuing each state using the time trade off method. Coefficients are derived for each level of each attribute using regression, which are combined as a decrement from a utility of 1.0 to give a utility for each state.

2.3.1 NSAID model

Disutilities for dyspepsia and GI bleeds were based on directly elicited utilities,[46,47] and the typical period of time patients would suffer symptoms for.[48] This is consistent with previous economic modelling methods,[49] and the disutility was calculated as follows:

$$(1 - utility\ of\ health\ state) \times \frac{Time\ in\ health\ state\ in\ days}{365\ days}$$

The disutility in the year following an MI was taken from a study reporting the annual utility loss associated with various cardiovascular events adjusted for patient characteristics using regression methods.[50] As evidence was conflicting regarding whether there was a long-term quality of life

impact following an MI,[51,52] the most conservative estimate in the literature of MI disutility in subsequent years was applied, and a wide distribution was used in probabilistic sensitivity analysis to reflect the uncertainty around this value.[53]

2.3.2 Benzodiazepine model

The most robust estimates of utility loss following fractures are from two systematic reviews and one Swedish study which uses three different scenarios to analyse the disutility in the 12 months following various fracture types and were similar across these studies.[54–56] The disutility for hip fracture was taken from the systematic review which included the greatest number of studies, and the utility loss in the year following a wrist fracture from this study was applied to the other fall injury state.[56] A disutility was applied to all residential states, consistent with previous economic models relating to hip fractures, on the basis that individuals who are institutionalised are likely to have some impairment in the dimensions captured by the EQ-5D such as mobility, self-care, or usual activities.[57,58] The input used was based on the utility difference between carers of Alzheimer's disease patients in the community and in nursing home residence.[59]

2.3.3 PPI model

The disutility of hip fracture and residence in a nursing home were the same as those used in the benzodiazepine model. The disutility of a case of *C. difficile* does not seem to have been directly elicited in any study using the EQ-5D or time trade off methods. The annual utility loss due to *C. difficile* was based on the utility of being hospitalised and the likely duration of hospital stay, calculated using the equation above.[60,61]

Table A 1 Point estimates for each parameter input and distributions used in probabilistic sensitivity analysis

Parameter description	Value	Distribution	Source
NSAID model			
Transition probabilities			
Probability of dyspepsia in non-NSAID users	0.0497	Beta (4,058, 75,513)	[10,11]
Probability of GI bleed in non-NSAID users	0.0013	Beta (99.71, 76,601.91)	[12,13]
Probability of death following GI bleed by age group		Beta	[64]
60-79	0.11	(156, 1,265)	
80+	0.2	(174, 698)	
Probability of an MI in non-NSAID users	0.0082	Beta (419, 50775)	[16]
Probability of an MI in the 12 months following an MI	0.064	Beta (2339.94, 34221.56)	[4]
Probability of an MI in subsequent years after an MI	0.0143	Beta (1378.65, 95030.28)	[4]
Probability of death following an MI	0.097	Beta (209, 1942)	[17]
Probability of death by age group			
65-69	0.0121		[65]
70-74	0.0198		
75-79	0.0340		
80-84	0.0644		
85+	0.1495		
Effect			
Relative risk of dyspepsia in long-term NSAID users	1.4	Log-normal (0.336, 0.126)	[10,11]
Relative risk of GI bleed in long-term NSAID users	3.07	Log-normal (1.122, 0.114)	[13]
Relative risk of MI in long-term NSAID users	1.53	Log-normal (0.425, 0.174)	[13]
Relative risk of death in people >1 year post-MI	2	Log-normal (0.693, 0.088)	[4]
Utility			
Utility of being in well state		Beta	
65-74	0.77	(129.13, 38.57)	[66]
75+	0.74	(108.51, 38.13)	
Utility decrement in 12m following dyspepsia	0.0325	Gamma (129.13, 38.57)	[46,47,49]
Utility decrement in 12m following GI bleed	0.0433	Gamma (108.51, 38.13)	[46,47,49]
Utility decrement in 12m following MI	0.055	Gamma (74.37, 1352.24)	[50,51]
Annual utility decrement >12m post-MI	0.012	Gamma (4, 333.33)	[51–53]
Costs			
Cost of NSAID treatment	149.64	Gamma (100, 0.668)	[67]
Cost of paracetamol treatment	97.68	Gamma (100, 1.024)	[67]
Cost of managing dyspepsia	152.64	Gamma (100, 0.655)	[67]
Cost of managing a GI bleed	4,983.68	Gamma (44.44, 0.009)	[36,37,67]
Cost of managing an MI	9,856.67	Gamma (100, 0.010)	[3,36,38]
Cost of a previous MI	819.56	Gamma (100, 0.122)	[3,67]
Benzodiazepine model			
Transition probabilities			
Probability of an injurious fall requiring healthcare utilisation		Beta	[22–25]
65-79	0.0476	(95, 1,905)	
80+	0.1	(200, 1,800)	
Probability of a hip fracture		Beta	[7]
65-69	0.0014	(197, 140,517)	
70-74	0.0031	(357, 114,804)	
75-79	0.0066	(597, 89,858)	

Parameter description	Value	Distribution	Source
80-84	0.0152	(961, 62,263)	
85+	0.0247	(1,071, 42,289)	
Probability of being in nursing home at 12m following a hip fracture	0.11	Beta (224, 1,810)	[21]
Probability of being admitted to nursing home in general population			[32]
		Beta	
65-69	0.0021	(301, 143,095)	
70-74	0.0033	(393, 118,759)	
75-79	0.0065	(601, 91,865)	
80-84	0.0151	(980, 63,904)	
85+	0.0241	(1,093, 44,254)	
Effect			
Relative risk of an injurious fall in long-term benzodiazepine users	1.553	Log-normal (0.440, 0.043)	[26]
Relative risk of injurious fall in 12 months post-fall injury	2.0	Log-normal (0.693, 0.039)	[6]
Relative hazard of death in 12 months following a hip fracture relative to people without fracture	3.26	Log-normal (1.182, 0.062)	[31]
Utility			
Utility decrement in 12m following a hip fracture	0.203	Gamma (209.33, 1,031.2)	[55,56]
Utility decrement in 12m following other fall injury	0.06	Gamma (22.13, 368.79)	[55,56]
Utility decrement of being resident in nursing home	0.06	Gamma (0.58, 9.72)	[57–59]
Costs			
Cost of benzodiazepine treatment	77.92	Gamma (100, 1.283)	[67]
Cost of hip fracture	17,394.47	Gamma (385.34, 0.022)	[5,20,67]
Cost of other fall injury	2,782.39	Gamma (25, 0.009)	[5,7,8,67]
Cost of residence in nursing home	42,670.00	Gamma (9,407.98, 0.220)	[45]
PPI model			
Transition probabilities			
Probability of having *C. difficile* infection	0.00358	Beta (1839, 511,848)	[9]
Effect			
Relative risk of hip fracture in maximal dose PPI users relative to non-users	1.462	Log-normal (0.380, 0.097)	[34]
and maintenance dose PPI users relative to non-users	1.247	Log-normal (0.221, 0.050)	
Relative risk of *C. difficile* infection in maximal dose PPI users relative to non-users	2.349	Log-normal (0.854, 0.140)	[35]
and in maintenance dose PPI users relative to non-users	1.735	Log-normal (0.551, 0.114)	
Relative hazard for death in 12m post *C. difficile*	1.23	Log-normal (0.207, 0.089)	[33]
Utility			
Utility decrement in 12m post *C. difficile*	0.026	Gamma (0.530, 20.38)	[60,61,63]
Costs			
Cost of max dose PPI treatment	160.80	Gamma (25, 0.155)	[67]
Cost of maintenance dose PPI	117.12	Gamma (25, 0.213)	[67]
Cost of *C. difficile*	5,837.32	Gamma (19.3, 0.003)	[9,39,40]

3 TreeAge Pro model structures

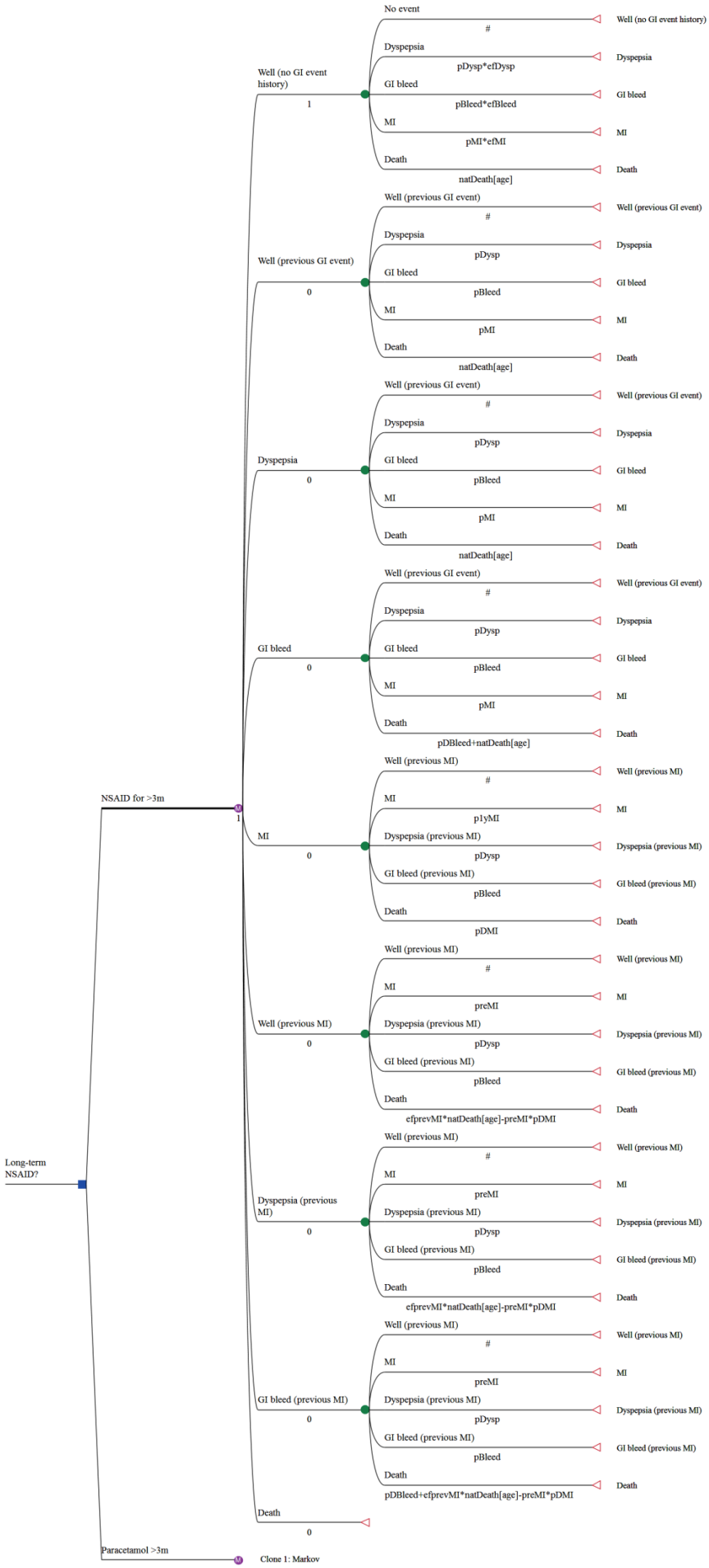

Figure A 2 Decision tree structure for NSAID Markov model in TreeAge Pro

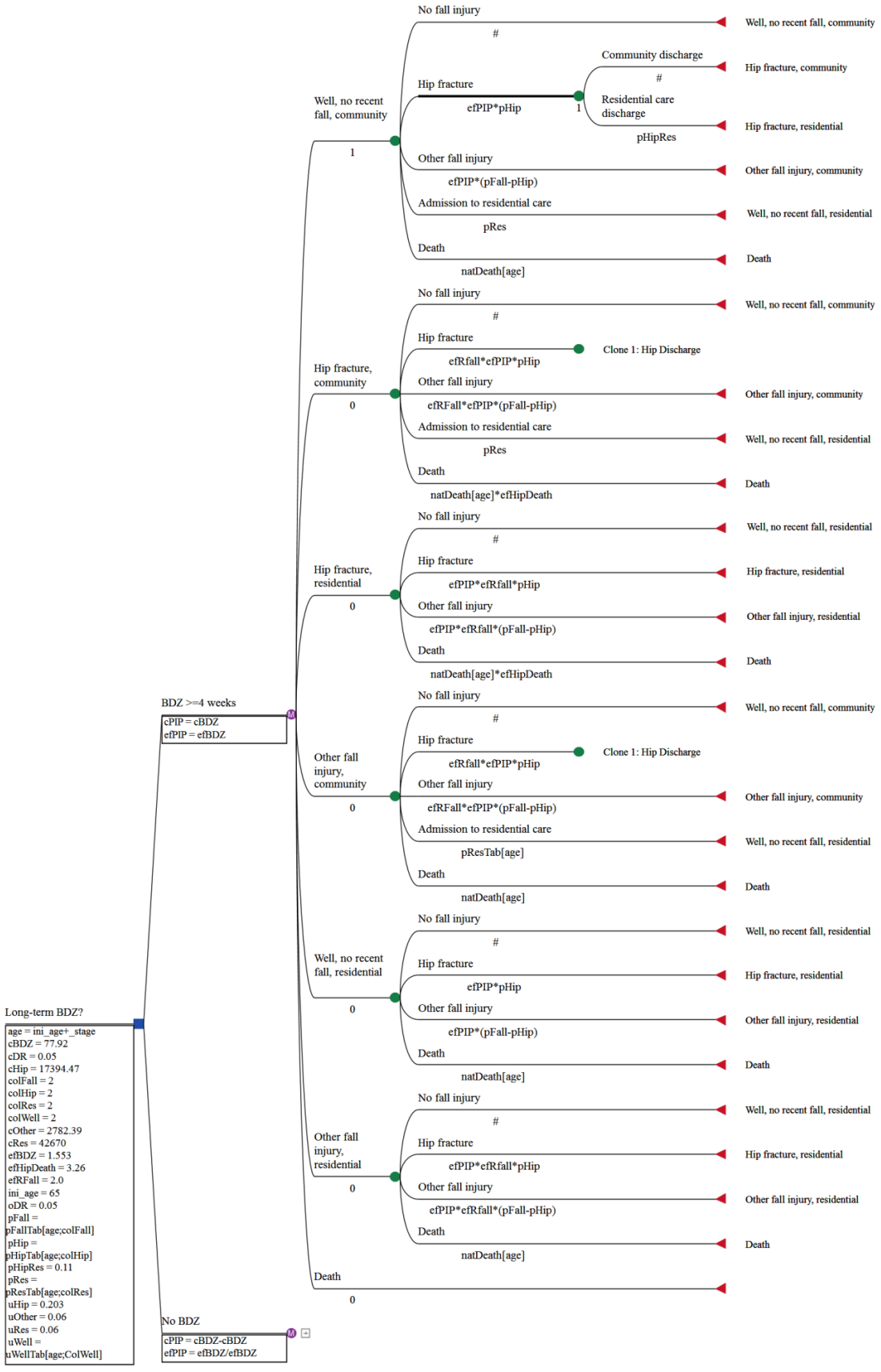

Figure A 3 Decision tree structure for benzodiazepine Markov model in TreeAge Pro

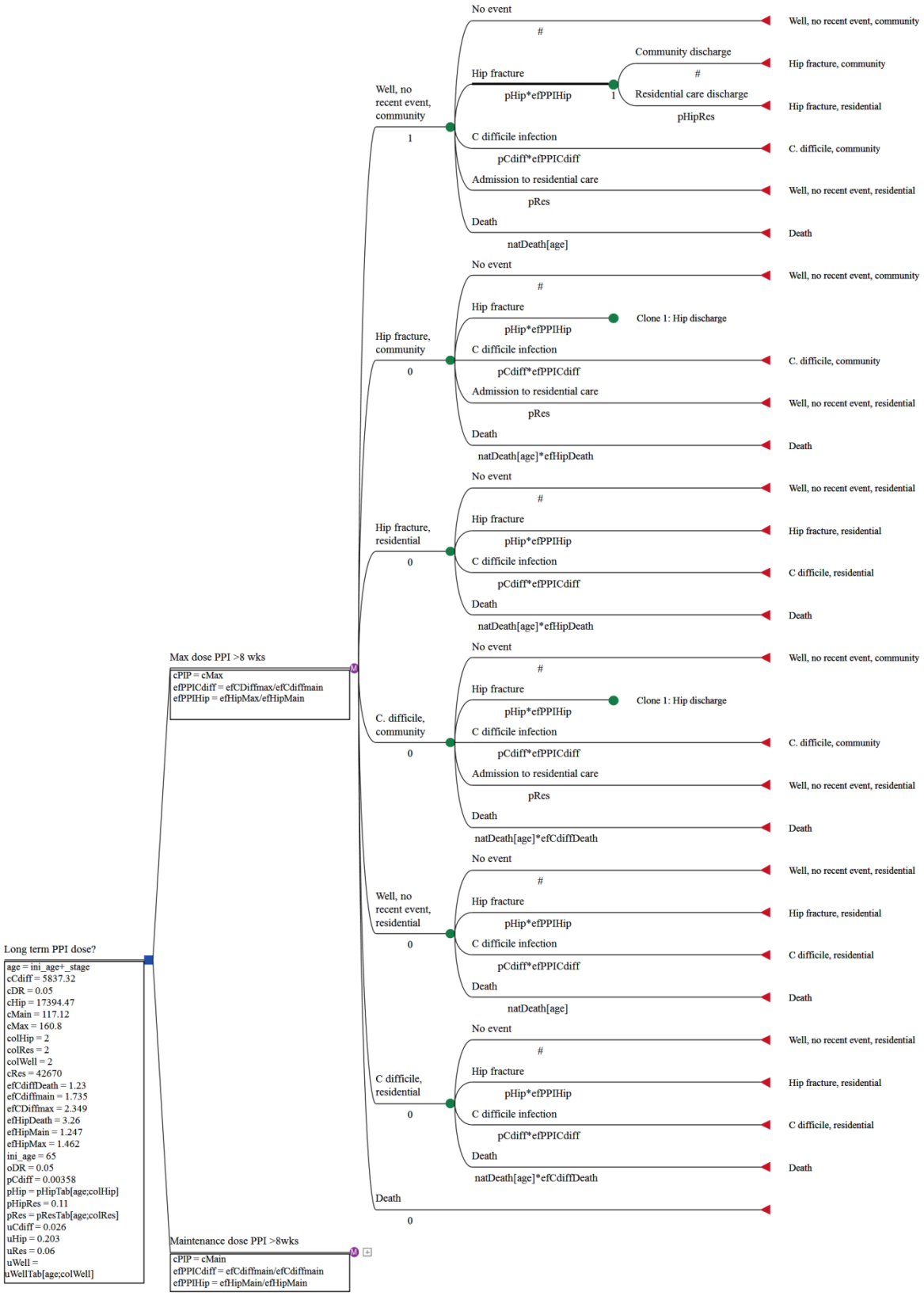

Figure A 4 Decision tree structure for PPI Markov model in TreeAge Pro

4 Probabilistic sensitivity analysis methods

Uncertainty associated with imprecision of the parameter inputs was incorporated into the model using probabilistic sensitivity analysis (PSA) to allow 95% credible intervals (CIs) to be fitted. A distribution of possible values for each parameter was specified, which were fitted under the assumption of a homogenous sample of patients informing parameter estimates (i.e. heterogeneity between patient sub-groups was not investigated). The distribution type used for each parameter reflected the form of data the parameter takes and the standard distributional assumptions used when estimating CIs (as detailed below).[38] The distributions fitted for each parameter were calculated from data available in published sources and these are reported in Table A 1. Each model was run over 10,000 iterations and a random value for each parameter input was sampled from the specified distribution for each run. The outputs of each iteration were recorded to provide a distribution of cost and effect differences and the 2.5th and 97.5th percentiles for these differences were used to estimate 95% CIs. Statistical significance was assumed if the 95% CI for the incremental costs and effects did not include zero. The outputs of each iteration were also plotted on a cost-effectiveness (CE) plane to compare the distribution of ICER estimates for each PIP.

4.1 Approaches used to specify distributions for parameters

4.1.1 Probability parameters

As probabilities can only range between zero and one, the distribution specified must adhere to this limit so that impossible values are not selected from the distribution. A beta distribution is suitable for binomial data as it is constrained between zero and one. It is characterised by two parameters, α and β. In a single study where the number of events and sample size are known, the value of α can be set to the number of events and β to the sample size minus the number of events to specify the beta distribution for uncertainty around the probability point estimate. In the absence of this information, for example if using findings from a meta-analysis, the distribution can be fitted by the method of moments if the mean or proportion and standard error or variance are given, using the following equations:

$$\alpha = \bar{\mu}\left(\frac{\bar{\mu}(1-\bar{\mu})}{s^2} - 1\right),$$

$$\beta = \alpha.\frac{(1-\bar{\mu})}{\bar{\mu}}.$$

4.1.2 Relative risk parameters

Relative risks (RR) are composed of ratios of ratios ranging from zero to infinity and the confidence intervals for which are calculated on the log scale. Therefore, the appropriate distribution for these parameters is lognormal and a distribution can be specified as N(ln[RR], se[ln(RR)]), by taking the natural log of the point estimate and calculating the standard error of this using reported Cis as follows:

$$se[\ln(RR)] = \frac{\ln(Upper\ CI) - \ln(Lower\ CI)}{2 \times 1.96}.$$

4.1.3 Cost parameters

Cost data is constrained to positive values so is generally truncated (to exclude negative values) and right-hand (or positively) skewed as there tends to be small numbers of cases with high costs on the right side of the distribution. Often Poisson or gamma distributions are used to represent cost data, although lognormal distributions can also be used. A gamma distribution can be fitted with the method of moments. For gamma(α,β), the mean ($\bar{\mu}$) is equal to αβ and the variance (s^2) is equal to $\alpha\beta^2$, which can be rearranged to:

$$\alpha = \frac{\bar{\mu}^2}{s^2},$$

$$\beta = \frac{s^2}{\bar{\mu}}.$$

4.1.4 Utility parameters

Utility parameters tend to fall within the range zero to one, however they can technically range into negative values, representing states worse than the reference 'worst health state' used to derive them (usually death). For utilities far from zero, a beta distribution can be used. Another approach is to use the disutility or utility decrement for a health state (1 – utility), which are constrained between zero and positive infinity and can be specified as gamma or lognormal distributions.

In this analysis, we used a beta distribution for the utility in the 'Well' state using the approach outlined in section 3.1.1, and gamma distributions for disutilities using the approach outlined in section 3.1.3.

5 Published estimates of intervention effectiveness

In the OPTI-SCRIPT trial of a complex intervention in general practice, the relative risk of being on a long-term maximal dose PPI post-intervention was 0.45 (i.e. a 55% reduction) compared to usual care.[68] For NSAIDs, a recent trial of education, informatics and incentives in general practice demonstrated a significant reduction of 49.8% in high-risk prescribing relating to NSAIDs and gastroprotection (i.e. a risk reduction of 0.498).[69] A trial to reduce inappropriate prescribing of benzodiazepines using direct patient education demonstrated an additional 23% of those in the intervention group had discontinued benzodiazepines compared to control (i.e. a risk reduction of 0.23).[70]

In the economic evaluation of potential interventions to reduce PIP, a new decision was framed between implementing an intervention to reduce PIP or usual care, as illustrated in Figure A 5 below for NSAIDs. The effectiveness estimate of the published interventions for each type of PIP was used as an input in each analysis as the proportion of patients receiving the intervention who are switched from the PIP drug to the more appropriate alternative.

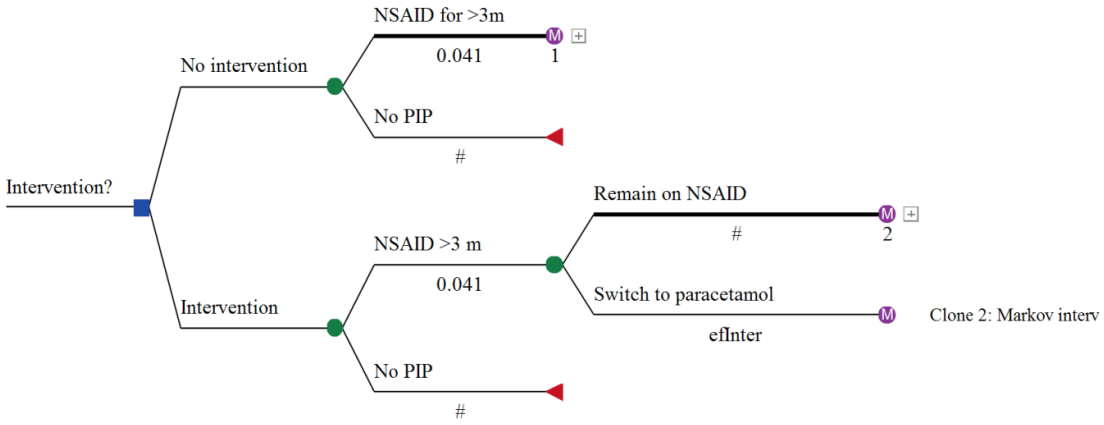

Figure A 5 Decision tree structure of published intervention analysis for NSAIDs

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Appendix 3 – Supplementary results of economic evaluation analysis

Base case analysis

Table A 2 Number of adverse events for PIP and non-PIP scenarios

Adverse events	PIP cases	Non-PIP cases	Difference	NNH
NSAID model				
GI bleeds	48	25	23	43
Dyspepsia	1141	973	168	6
MIs	213	172	41	25
Benzodiazepine model				
Hip fractures	296	184	113	9
Other injuries	1864	1159	704	1.4
PPI model				
Hip fractures	195	167	28	36
C. difficile infections	94	70	24	41
Adverse events	PIP cases per 1000 person years	Non-PIP cases per 1000 person years	Difference	NNH
NSAID model				
GI bleeds	60.34	50.91	9.44	106
Dyspepsia	2.54	1.30	1.24	804
MIs	11.24	9.00	2.24	447
Benzodiazepine model				
Hip fractures	15.22	9.44	5.78	173
Other injuries	95.74	59.56	36.18	28
PPI model				
Hip fractures	10.04	8.59	1.45	689
C. difficile infections	4.84	3.57	1.27	791

Abbreviations: NNH, number needed to harm; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; QALYs, quality-adjusted life years.

Probablistic sensitivity analysis

The outputs of each iteration of the probabilistic sensitivity analysis were plotted on a CE plane to compare the distribution of ICER estimates for each PIP. Figure A plots the outputs for each iteration using the alternative NSAID scenario where individuals taking NSAIDs remain on this medication following any adverse event as opposed to the base case analysis where individuals are switched to paracetamol following an adverse event. This scenario was more comparable to the PPI and benzodiazepine models where in the base case analysis it was assumed that individuals remained on therapy regardless of adverse events, due to unlikely attribution of the adverse events in the case of PPIs and dependence and withdrawal effects in the case of benzodiazepines.

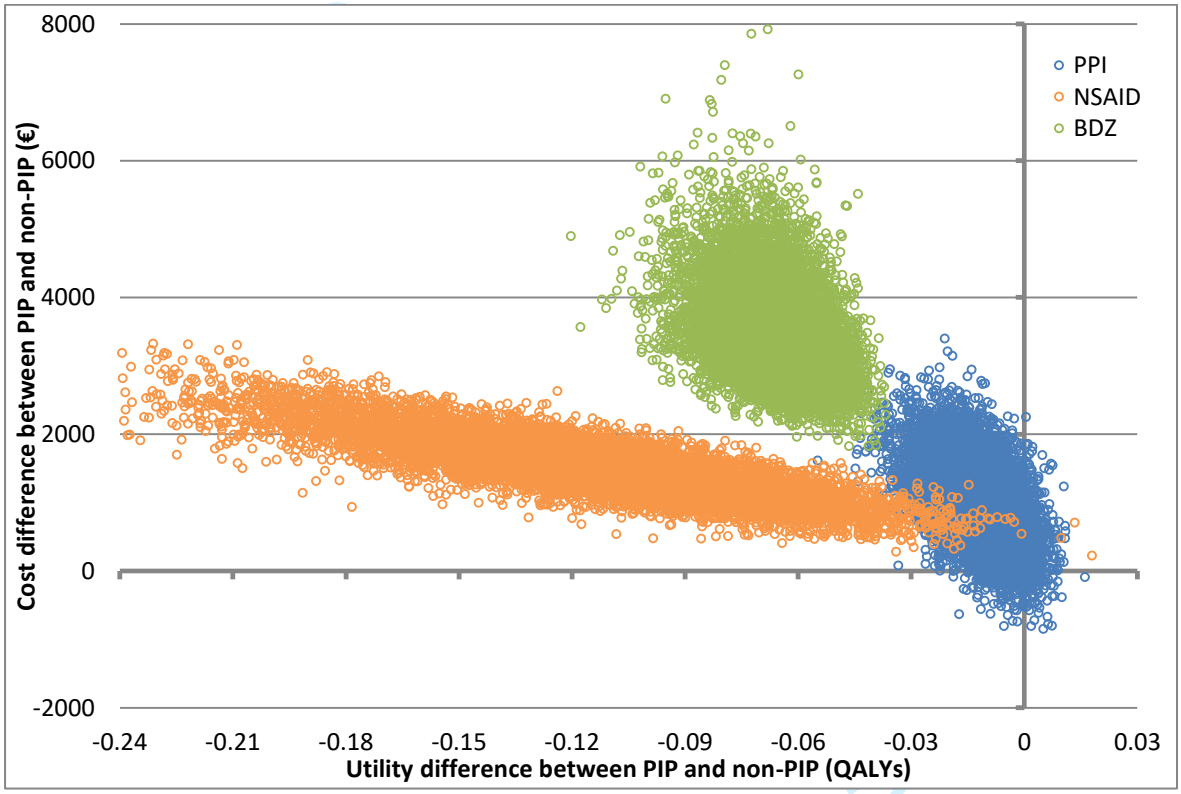

Figure A 6 Incremental costs and utilities for PIP compared to non-PIP from probabilistic sensitivity analysis using alternative NSAID scenario

Evaluation of cost-effectiveness of published interventions

The results of threshold analysis for an intervention to target NSAID prescribing are plotted in Figure A 7 showing whether the intervention is preferred to no intervention at a cost-effectiveness threshold of €45,000 per QALY as intervention cost and effectiveness vary. The arrow shows how an intercept can be used to determine the cost at which the intervention becomes cost effective given a certain effectiveness, or vice versa. For example, at a €500 intervention cost, the intervention targeting NSAID prescribing would be cost effective if it reduces PIP by at least 12.6%.

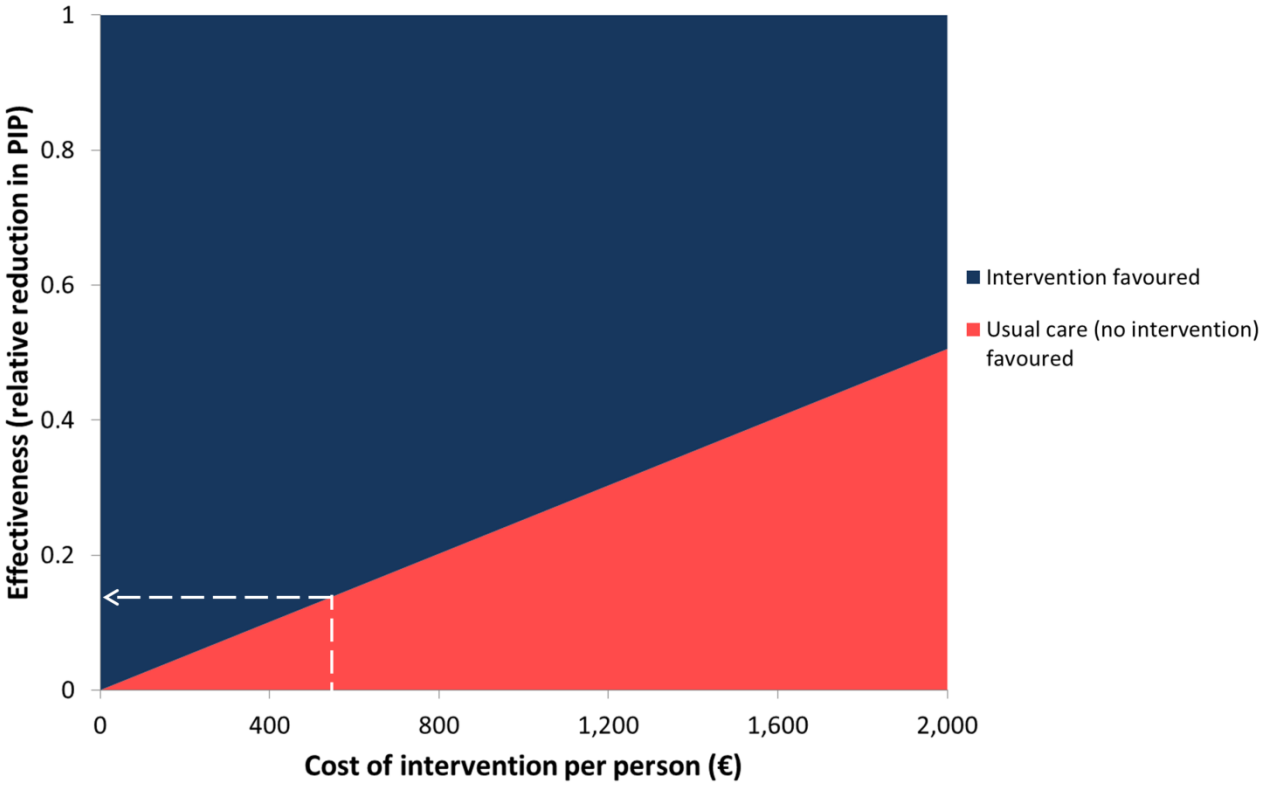

Figure A 7 Threshold effectiveness value for NSAID intervention at intervention cost of €500 and cost-effectiveness threshold of €45,000 per QALY