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Title

Expected benefits and budget impact from a microsimulation model support the prioritisation and implementation of Fracture Liaison Services

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Running title

FLS Benefit Calculator

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Disclosure of potential conflicts of interest

RPV received funding for this study from the International Osteoporosis Foundation and has received research grants from the UK NIHR and Kyowa Kirin Services, lecture fees from Astellas, and consulting fees from Amgen, Mereo Biopharma, UCB, and Kyowa Kirin Services. EB and CM have nothing to disclose. CC has received consulting fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic Merck, Novartis, Pfizer, Roche, Servier, Takeda, and UCB. MKJ received funding for this study from the International Osteoporosis Foundation, and has received research grants or contracts from UCB, Amgen, Besin Healthcare, and Sanofi.

Data Availability Statement

The data that support the findings of this study are available in the Supplemental Material and the code used to run the model is openly available in GitHub at https://github.com/cmaronga/OxfordUni.HEOR-FLSModel.

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Abstract

Osteoporotic-related fractures cause significant patient disability, leading to a growing burden on healthcare systems. Effective secondary fracture prevention can be delivered by fracture liaison services (FLSs), but these are not available in most countries. A major barrier is insufficient policy prioritisation, helped by the lack of economic assessments using national data and providing estimates of patient outcomes alongside healthcare resource use and cost impacts. The aim of this study was to develop an economic model to estimate the benefits and budget impact of FLSs and support their wider international implementation.

Five interconnected stages were undertaken: establishment of a generic patient pathway; model design; identification of model inputs; internal validation and output generation; and scenario analyses. A generic patient pathway including FLS activities was built to underpin the economic model. A state-based microsimulation model was developed to estimate the impact of FLSs compared to current practice for men and women 50 years or older with a fragility fracture. The model provides estimates for health outcomes (subsequent fractures avoided and quality-adjusted life years (QALYs)), resource use, and health and social care costs, including those necessary for FLSs to operate, over five years.

The model was run for an exemplar country the size of the United Kingdom. FLSs were estimated to lead to a reduction of 13,149 subsequent fractures and a gain of 11,709 QALYs. Hospital bed days would be reduced by 120,989 and surgeries by 6,455, whilst 3,556 person-years of institutional social care would be avoided. Expected costs per QALY gained placed FLSs as highly cost-effective at £8,258 per QALY gained over the first five years. Ten different scenarios were modelled using different configurations of FLSs. Further work to develop country specific models is underway to delivery crucial national level data to inform the prioritisation of FLSs by policy makers.

Keywords
Osteoporosis, Health Economics, Fracture prevention, Anabolics, Health Services Research

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Introduction

Osteoporotic-related fractures cause significant patient disability and reduce survival, leading to a substantial and growing burden on healthcare systems globally(1). Patients with a previous fragility fracture are at higher risk of subsequent fracture(2). Further, a recent major fragility fracture increases risk more in the imminent risk period as well as in the longer term(3-5). The clinical effectiveness of secondary fracture prevention is established. Randomised controls trials have demonstrated clinically significant reductions in fracture risk in those with recent major fragility fractures(6) and those at very high fracture risk(7,8). This is supported by real-world evidence studies that have demonstrated clinically significant reductions in major fractures by anti-osteoporosis medication in patients with a recent fracture (9). This has led to national(10,11) and international(12-16) initiatives to deliver effective secondary fracture prevention by implementing fracture liaison services (FLSs). FLS are small groups of healthcare professionals who identify, assess, recommend treatment, and monitor adults who are recently diagnosed with a fragility fracture to reduce their risk of another fracture (17). As expected, FLSs reduce the risk of subsequent fragility fracture in clinical studies (18,19) and reviews(20,21). Despite the expected increase in ageing populations leading to significant increases in fragility fractures(22), the majority of healthcare settings that manage adults with fragility fractures do not have FLSs in place. In the EU, many countries have no reported FLSs and where present, 50% of countries reported FLS coverage in less than 10% of hospitals (23).

A major barrier to FLS provision is the lack of policy prioritisation, especially in comparison with provision for other long-term conditions with similar secondary prevention strategies(1). In addition to considerations including local need and local healthcare capacity, understanding the benefits and budget impact of FLSs remains a key barrier. Policy makers need to prioritise secondary fracture prevention in relation to other global, national, and regional health priorities. Understanding the expected benefits as well as costs are critical to informing this decision making. Economic modelling studies have been widely employed to examine the cost-effectiveness of osteoporotic fracture prevention, but they have been limited not only by the use of less advanced techniques (24) but also by the paucity of national data, the flexibility of the patient pathway to reflect real-world patient journeys in terms of rates of identification, treatment recommendations and adherence, previous fracture and anti-osteoporosis medication history, variable outputs that include clinical events, healthcare use

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and costs, estimating the scale and type of FLS resources that would be needed, and finally independence from commercial bias.

The aim of this study was to develop an economic model based on an internationally applicable care pathway of individuals presenting with a fragility fracture and incorporating the key activities of FLSs to estimate their benefits and budget impact and hence support their wider international implementation.

Material and methods

The development of the model followed five interconnected stages: (1) establishment of a generic patient pathway; (2) model design; (3) identification of model inputs; (4) internal validation and output generation; and (5) scenario analyses.

Patient pathway

Following best practice guidelines for the development of economic models (25), previously published economic studies were reviewed to contextualise the modelling of costs and effectiveness of FLS programmes. Key elements of previous models were discussed with an international group of clinical FLS experts from Japan (n=4), Spain (n=4), and the UK (n=2) to ensure the patient care pathway for individuals presenting with fragility fractures was flexible enough to be adapted to different countries and healthcare systems.

Model design

With a generic patient pathway described in detail, the most appropriate target population, perspective of costs (i.e. costs to the payer as opposed to the patient, hospital, or society as a whole), health outcomes, resources used, costs, and time horizon that best served our specific aim, were identified as recommended by best practice guidelines (25). An economic model incorporating all relevant health states, events, transitions, interdependencies, use of health and social care resources, and costs was designed. The key activities of FLSs, namely (1) the proportion of hip, spine and other fragility fractures identified, (2) laboratory and bone density testing (3) anti-osteoporotic medication recommendations, and (4) monitoring to boost adherence were included in the model. This ensured the model was responsive to different FLS configurations. Comparators (i.e. the strategies being compared) were defined

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by our aim of estimating the impact of FLSs vis-à-vis current clinical practice, hence the model was run separately with inputs characterising "current practice" and then with those reflecting patient experience under an FLS. The difference in patient outcomes, resource use, and costs would then be interpreted as the impact of the FLSs. This allowed to run the model under different FLS configurations in the scenario analysis and compare how impacts varied. Once the model was conceptually designed, the simulation was coded in the R Programming language, defining all necessary input parameters and mathematical relationships to generate expected patient outcomes, resource use, and costs for each comparator.

Model inputs

Different methods were used to identify model inputs. For values that were considered applicable to any country such as anti-osteoporotic medication (AOM) efficacy and time to onset, published reviews of AOM efficacy were used. For inputs that were country-specific, we obtained values from (a) published literature; (b) government or other regional sources; or (c) consensus from national key opinion leaders (CC, MKJ) where no evidence was found. Key opinion leaders (KOLs) were asked to provide their expert opinion on the most conservative estimates.

The model was run for an exemplar country by populating it with international data for most inputs: general risk of re-fracture, healthcare treatment, social care, and FLS activities as well as treatment effects from the most used AOMs. To identify input values, the literature was reviewed and the most recent and reliable evidence on each model parameter identified, regardless of country. Where local data were needed such as the number of fragility fractures for the modelled cohort, evidence from the United Kingdom was used. Values from the literature were adapted to match model requirements and then confirmed with a group of expert KOLs. Where no evidence was found, the group was asked to provide their expert opinion on the most conservative estimates. Inputs on unit costs were identified in GBP (£) and corresponding to year 2021.

Statistical analysis and Internal validation

Once the model was populated with all required input parameters, both face and internal validations were conducted. For the former, input sources and confirmation that results correspond with reality was conducted in meetings with KOLs. For the latter, technical

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consistency and validity were examined by verifying equations, codes, and data against their sources by varying the values of key inputs one at a time and checking whether resulting outputs moved in the direction expected by clinical experts. For example, holding everything else constant, higher values of AOM effectiveness should lead to more fractures avoided and higher cost of hospitalisations should lead to higher total costs. Where this did not happen, code and formulae were reviewed and corrected to make sure all mathematical relationships were accurately captured.

Model outputs are reported as number of subsequent fractures, QALY gain, health care resources used (both inpatient and outpatient), social (formal home and long-term institutional) care, and associated costs by comparator. Each of these was further stratified by sex and sentinel fracture site. Costs and QALYs were discounted at 3.5% yearly rate to provide an estimate of the incremental cost-effectiveness ratio commonly used to inform decision-making in health.

Scenario analyses

Several scenario analyses were conducted to explore the ability of the model to capture the potential impact of implementing various FLS configurations based on clinical expertise. Analyses were run on target identification rates at 100% for all sentinel fracture sites, time to treatment initiation at 1 month, and monitoring rates at 100% at both 4 and 12 months after fracture reflecting published key performance indicators (17). Scenarios where AOM would be restricted for FLSs to alendronate only, injectables only, adherence of 100%, and a ‘perfect’ FLS with 100% identification, monitoring, and adherence simultaneously (purposely to be used as benchmark) were also explored. Finally, FLS models where only patients with hip fractures, or patients with either hip or spine fractures would be treated, were also simulated.

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 statement (26) was followed to make sure all relevant components of this economic assessment were reported appropriately and in a manner that is useful for decision making. The checklist of items of this statement is included in the Supplemental Material.

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Results

Patient pathway

A generic patient pathway specifically designed to include the key activities of FLSs was built to underpin the development of the economic model. No previously published economic model was found explicitly based on a patient pathway, but different aspects of the wider context of fracture prevention considered in those models helped inform the process. Figure 1 shows the pathway developed after several rounds of discussions with clinical experts and key opinion leaders from the United Kingdom, Japan, Mexico, the Netherlands, and Spain.

Figure 1 – Patient pathway

Sentinel as well as subsequent fractures were grouped into hip, spine, or major fractures in other sites. This was done to reflect the different patient pathways patients with these fractures can experience. Sentinel fractures could lead to hospital admission, generally via Accident & Emergency (A&E), although some such as spine fractures could be seen directly in an outpatient trauma clinic. After going through A&E, patients would be admitted or discharged, and if admitted they would receive either surgical procedures or non-surgical treatment. After discharge from hospital or the outpatient trauma clinic, some patients in certain settings might receive additional residential temporary rehabilitation, but they would all eventually be discharged either back to their own homes, with or without support from a caregiver, to the home of a relative, or to a residential care institution, more commonly after a hip fracture. At any stage of this pathway, patients face the risk of a subsequent fracture at any site as well as a risk of dying. The identification of patients to be included into an FLS could happen at any point, before or after clinical discharge, and in a proportion to be set in the respective model parameters as identification rates would vary by setting, fracture site, and potentially even sex.

Model design

The patient pathway described above underpinned the design of the economic model. As the aim of the model is to estimate the impact of FLSs, the target population was set to be men and women 50 years or older, as that is the age at which the likelihood of experiencing a fragility fracture starts to increase rapidly(27). To be able to inform public healthcare policy decisions, the base case analysis followed the perspective of the public healthcare payer;

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considering the significant impact of fragility fractures to hospitals as well as patients and their families, the model was designed so that it could also take the perspective of a hospital, another payer, or the broader society.

Model outputs were divided into three categories: health outcomes, resource use, and costs. Under health outcomes, the model reports the number of subsequent fractures by site and quality-adjusted life years (QALYs). Resources of interest were length of stay at hospital, number of surgical procedures, clinic appointments, number of temporary rehabilitation days, and time in institutional care. For the implementation of the FLS programme, the number of hours of staff needed, laboratory tests, and DXA scans were also included. Costs are reported in the model separately for those linked to hospital care (procedures, length of stay, and clinics), temporary rehabilitation, community care (for spine fractures or monitoring after discharge), social care (home support and institutional care), and those associated with the FLS programme (staff, tests, scans, and AOM). All the above are tracked in the model over a time horizon of five years, chosen based on the trade-off between length of the time horizon and the certainty of key inputs such as site- and sex-specific subsequent fracture rates. Five years provides a timeframe that allows to use good quality evidence on risk of subsequent fracture whilst at the same time providing policymakers with outputs within a relevant time-period for their political decision-making.

Model structure

The model was designed as a state-based microsimulation (schema shown in Figure S1 of the Supplemental material), with monthly cycles. As people experiencing a fragility fracture enter the model, in each cycle they can either die, suffer a subsequent fracture (in any site), or spend the cycle without any further fracture. The choice was guided by evidence on the time-varying association between risk of subsequent fracture and recency of the sentinel one (5,28-30). This imminent fracture risk has been shown to lead to potentially significant impacts on the benefits of FLSs (31). The choice of a microsimulation design is justified by the impact of a patient prior history of fractures on their risk of a subsequent fracture, mortality, and quality of life.

Model logic

Simulated individuals of a given sex (male, female) and fracture site (hip, spine, other) enter the model immediately after their sentinel fracture and can move into the fracture-free state or experience a subsequent fracture in the same or another site.

Each time a simulated individual moves into a subsequent fracture state, events from the patient pathway in Figure 1 are randomly assigned based on inputs. That is, attending hospital or an outpatient trauma clinic (for patients with spine fracture), hospital admission, having a surgical procedure, discharge to temporary rehabilitation, and ultimate discharge destination are all randomly assigned based on probability inputs. This also applies to FLS activities, with different values applied to 'current practice' or the 'FLS' strategy. A flow diagram for FLS identification is shown in the Supplemental Material Figure S2.

Each subsequent fracture is followed by the individual facing a probability of being identified and potentially recommended an AOM. If a change of prescription occurs, it would happen only for one of equal or superior strength. Some AOMs have limits to how long patients can take them: zoledronate can only be taken for up to three years continuously, abaloparatide and teriparatide for two, and romosozumab for up to one. In each case, patients could be allocated to no treatment or to any other eligible AOM. More details about the logic behind treatment assignment and a corresponding flow diagram are shown in the Supplemental Material (Figure S3 for the latter).

For treatment adherence, an individual is assigned to being an adherer or non-adherer to their AOM at time of prescription based on probability inputs. Those that are adherent can then become non-adherent at 4, 12, or 24 months, when adherence is reassigned based on probabilities by AOM and sex, if relevant. Supplemental Material Figures S4, S5, and S6 illustrate the logic for primary and 4-month adherence, as well as the flow diagram for 4-month monitoring.

Each AOM is associated with a specific relative risk reduction for subsequent fracture and to a time lag, expressed in months, denoting the period between treatment initiation and when the relative fracture risk reduction is applied. An individual must be adhering to the medication for any associated relative reduction to be applied. Figures S7 and S8 in the

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Supplemental Material illustrate the logic behind the application of treatment effect after sentinel fracture and after a further fracture, respectively.

Average age at time of sentinel fracture is an input of the model and is used for all-cause mortality. Fracture-related risks of mortality depend on site of fracture. After a hip or spine fracture, risks of mortality are drawn from inputs. After a fracture in another site, risks of mortality are based on population life tables specific to the country of interest. After a subsequent fracture, the risk of mortality is taken from the highest of either 1) the continuation of the risk given their latest fracture, or 2) a new risk based on their subsequent fracture.

QALYs are estimated by applying a health utility decrement every time a fracture occurs, and a progressive improvement afterwards. Starting health utility levels immediately after the sentinel fracture as well as decrements and improvements were taken from an international study reporting on 18-month follow-up of patients after hip, spine, and forearm fractures (32). As the model allows for more than one fracture and recovery does not reinstate individuals to their original health utility levels, we applied the proportion of potential change (33) implicit in the original study using the lowest health utility as a reference for decrements associated with a subsequent fracture.

Further details about the logic of the model are included in the Supplemental material.

Assumptions

In addition to the assumptions associated with the model structure and logic as described above, it is assumed that individuals are treatment-naive when entering the model, hence they can be assigned to any of the AOM in the first instance. Also, no more than one fracture was allowed in a given month; non-hip non-spine fractures are assumed not to lead to excess mortality beyond baseline all-cause risk of death; and health utility remains constant after 18 months post-fracture, unless another fracture occurs.

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Model inputs

The model requires inputs that characterise the trajectory of patients over the pathway shown in Figure 1 under current practice and under the assumption FLSs would be widely implemented. Each of these strategies had their corresponding mean transition probabilities, use of resources, and costs. One of the key inputs of the model is the risk of a subsequent fracture as experienced by people not under treatment, so that a relative risk can then be applied when the patient is under treatment and adherent to it, as explained in the model logic. These fracture rates are obtained at 5 or 10 years, depending on availability, and then monthly probabilities estimated based on previously reported 10-year non-linear progression of subsequent fractures in men and women following individual sentinel fractures (5). Table 1 lists several key inputs feeding the model for both current practice and FLS for the exemplar country used for this analysis. International values were obtained from the literature, estimated, or identified by KOLs. These, together with their respective sources, are shown in the Supplemental Material for all inputs.

Table 1 – Selected key model input parameters for base case

Internal validation and results

To estimate population-level outcomes and budget impact, the model was run for a given number of simulations and results scaled to the size of each of the six cohorts (3 fracture sites x 2 sexes). The model was run for a country of the size of the United Kingdom, with the following number of expected sentinel fragility fractures in a given year: 16,826 spine, 22,434 hip, and 72,911 other major fractures for men, and 33,651, 44,868, and 145,812, respectively, for women. Health outcomes, resource use, and costs were generated scaling the results from the number of simulations to the specified cohort sizes. The number of simulated individuals considered sufficient to run the model was taken to be the number after which the expected number of re-fractures for each comparator remained stable. This was reached at 75,000 simulated individuals per cohort, totalling 450,000 simulated individuals per comparator (900,000 in total), before scaling to produce outputs for the specified cohorts. Health outcomes, resource use, and costs were generated by cohort for each comparator, with the differences representing the impact of FLSs and reported by sentinel fracture site, sex, and overall.

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Internal validation was conducted by running the base case model multiple times, first with the set of input parameters (reported in the Supplemental Material), and subsequently by increasing and decreasing the values for average age, re-fracture rate, treatment rate, case identification, time to treatment initiation, treatment effect, adherence rate, monitoring rate, mortality rate, % of patients receiving a procedure, time spent by stage of secondary fracture prevention, unit costs of AOM, and discharge destination, one at a time. Expected impacts from each change in input parameters were contrasted with corresponding model outputs. Coding errors or shortfalls were identified and corrected until all changes in parameters led to expected changes in outcomes. Final results were discussed with KOLs and face validity was confirmed.

A summary of the health outcomes under current practice compared to FLS is shown in Table 2. Based on model input parameters and model assumptions, the implementation of FLSs would avoid 13,149 subsequent fractures over the first five years of FLS implementation. Avoided non-hip non-spine fractures accounted for 48% of the total, with those of the hip and spine accounting for 36% and 16%, respectively. Avoiding these subsequent fractures would lead to a gain of 11,838 QALYs over this period.

Table 2 – Health outcomes, resource use, and costs from FLS implementation

Health and social care resource use and costs for current practice and FLS are also shown in Table 2. As reported in the table, FLSs would lead to a reduced demand for healthcare provided at the hospital and community, reflected in the lower numbers of surgeries, hospital bed days, clinic appointments, and rehabilitation. This would be due to the reduction in subsequent fractures as a direct result of the services provided by FLSs, which would require increased resources in the form of FLS staff, DXA scans, and laboratory tests, as shown in the table. FLSs would lead to a shift in patient-facing time from doctors towards FLS administrators and coordinators, often provided by nurses and other health-related roles.

The model shows that fractures avoided also mean the number of people requiring institutional care due to their diminished independence would decrease. Both, the expected number of patient years in institutional care and the number of patients ever to require moving into them would drop if FLSs are implemented (by 3,556 and 1,910, respectively), as shown in Table 2.

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In terms of costs, as with resource use, FLSs would lead to savings of health and social care funding associated with the treatment of and care for people after fractures, with an expected increase in the costs of FLS prevention services. As shown in Table 2, there would be an expected cost savings of £69.2 million from healthcare services, mainly from the number of surgical interventions avoided (accounting for 50% of total healthcare savings) and temporary rehabilitation (43%). Social care services also report expected savings of an additional £36.6 million. Whilst savings from long-term institutional care would be expected to reach £130 million, many people avoiding a subsequent fracture and institutional care as a result would still require formal care at home, leading to an estimated cost increase of £93.3 million, yet leading to an overall savings in social care overall. The cost impact of providing the FLS services responsible for the above savings are also reported in Table 2. AOMs make up 82% of the costs of running the modelled FLS. Overall, the implementation of FLS programmes lead to a 5-year additional investment of £96.7 million (discounted over time). This represents 0.4% of the total costs estimated to be incurred under current practice, which combined with the expected QALY gains would lead to an incremental cost-effectiveness ratio of £8,258 per QALY over the first five years of FLS implementation.

Figure 2 shows the yearly extra (undiscounted) costs and QALYs gained by implementing FLS compared to current practice over the 5-year time horizon of the model. For this cohort analysis, extra costs are concentrated on the first year, with these dropping significantly thereafter. Gains in QALYs increase over time as each fracture avoided generates a gain compared to having had a fracture, a benefit that extends over time until the person dies.

Figure 2 – Extra costs and QALYs of FLS compared to current practice by year

Scenario analyses

Table 3 reports the main results of the model for the 10 different scenarios examined reflecting various configurations of FLSs. In all cases, specific changes were made as reflected in scenario titles whilst keeping all other FLS inputs constant to examine the impact of the specific change being investigated.

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FLS identifying all fragility fractures would lead to more fractures avoided and more QALYs gained at a slightly higher cost compared to the FLS base case, hence producing a better (lower) ratio of extra cost per QALY gained. Starting treatment one month after sentinel fracture would also represent an improvement compared to the FLS base case though only slightly. FLS costs would be £3 million higher as patients would be on treatment for longer. Compared to the base case, FLSs monitoring all patients would lead to more fractures avoided and more QALYs gained at similar levels to initiating treatment at 1 month, but at overall costs lower than in the base case, which already has a monitoring rate of 80%.

An FLS strategy of interest would be to provide patients with injectable AOMs only, given their higher adherence and generally higher effectiveness. We explored two such scenarios: one with clinical criteria that considered both effectiveness and costs (‘standard’), and a second one where the most effective injectables were chosen regardless of costs (‘maximum reduction’). Both were significantly more costly (FLS costs and overall), but they also improved health outcomes compared to FLS base case. As expected, the ‘max reduction’ scenario led to higher number of fractures avoided vis-à-vis current practice but at significantly higher FLS operation costs than ‘standard’ injectables only. This was reflected in a nearly double incremental cost-effectiveness ratio of £49,201 per QALY gained under the injectables only ‘max reduction’ scenario compared to £27,452 under ‘standard’ injectables only. In contrast, if FLSs recommended only the use of alendronate, they would reduce fractures by only 10,993 but at such low costs that, considering overall health and social care cost impacts, FLSs would have dominated current practice, i.e. resulted in gains in QALYs whilst being cost-saving at the same time.

Keeping pharmacologic prescriptions as used in the FLS base case but rising adherence to 100% would increase fractures avoided and QALYs gained over the base case and lower costs, leading to a more favourable cost per QALY of £7,055. Considering FLSs that simultaneously achieved 100% identification, treatment initiation at 1 month, 100% monitoring, and 100% adherence (“Perfect FLS” scenario) would produce the best results of all in terms of health outcomes (fractures avoided and QALYs), at a cost per QALY of £5,785. FLS costs would be slightly higher than the base case, but overall costs would be lower. Finally, we explored two more scenarios where only hip, or only hip and spine fragility fractures would be treated in FLSs. They both expectedly led to significantly lower numbers of factures avoided, although treating only hip and spine fractures would reduce

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subsequent fractures by 13% of those estimated under a current practice that treated hip and spine fractures only as well, the highest expected change reported by all scenarios examined. Both scenarios reported lower overall costs, hence becoming dominant over their respective current practice comparator.

Table 3 – Model results for different FLS configurations

Discussion

We stablished a patient pathway for people having fragility fractures which summarises the main events and contacts with the health and social care systems and has the flexibility to be adapted and used in different countries. A scope of the literature for its development found no previous models reporting an explicit patient pathway underpinning the economic model. The pathway developed for this model furthermore highlights the importance of social care after a fragility fracture given the significant amount of time patients spend receiving social care compared to health care.

The model developed in this study uses microsimulation methods to estimate the incidence of subsequent fractures and their QALY impact on men and women who have had a previous fragility fracture, all relatively common features of previously published osteoporosis models(34-37). However, the model presented here is novel in that it uses a 1-month cycle which allows to incorporate imminent risk of subsequent fracture; it accounts for time to treatment initiation, time for treatment to take effect depending on the AOM prescribed, and adherence to the specific drug, all critical to accurately estimate the incidence of subsequent fractures and the impact of programmes that prevent them. The model is also unique in that it is centred on assessing the benefit and budget impact of FLSs by including as part of the pathway and microsimulation the key activities of FLSs, i.e. patient identification, assessment, treatment, and monitoring. The model reports key data for decision makers, including the number of staff, laboratory and bone density testing, and medication costs required for FLS implementation. Finally, the model permits an FLS to enter its current performance data to understand the expected impact on patient, healthcare resource, and economic outcomes, and where to focus service improvement.

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Many inputs are needed to run the model and these are expected to be obtained from various sources, with emphasis on local data if available, followed by evidence from neighbouring countries if found acceptable to local experts, international evidence for those inputs generalisable across countries, and local expert opinion otherwise. For this study and for all future application of this model, iterative discussion and validation of inputs with local experts is a priority, not only for the face validity of results but also because of its directed aim to support local decision making for the implementation of FLSs. The identification of inputs to run this model for any setting would place a significant burden on analysts, given its complexity and large number of elements it considers. Whilst other calculators offer simpler structures that require considerably fewer inputs(38), the model described here offers benefits the simpler models can't which are relevant to policy makers such as disaggregation of results by sex and fracture site, proportion of cohort benefiting from the application of relative risk reduction from medication intake over time, impact of adherence, and detailed estimated resource use and costs of health and social care, amongst others.

By generating estimates of fractures avoided and QALYs gained, as well as savings in healthcare resource use, extra resources needed to provide the prevention services (healthcare staff, tests, scans), and cost implications, this model can comprehensively inform decisions around FLS implementation. The ability of the model to assess the benefit and budget impact of different configurations of FLSs, known to vary substantially amongst different settings, will particularly facilitate the decision-making process.

For the base case examined in this study, model results using international data as inputs for a country the size of the United Kingdom showed that a FLS programme would lead to a reduction of 13,149 subsequent fractures and a gain of 11,709 QALYs over its first five years of operation. This would also free important levels of health and social care services and funding which would otherwise have been needed for the care of individuals having subsequent fractures. Expected extra costs per QALY gained placed FLSs as a highly cost-effective intervention at £8,258 per QALY gained over the first five years, which compares highly favourably with the cost-effectiveness threshold of £20,000 to £30,000 per QALY gained used in England or the US$50,000 commonly used in many other countries. Furthermore, model results make explicit that whilst extra costs are concentrated on the first year for a static cohort, gains in QALYs would continue to grow over time. The former is explained by the prevention investment required at the start of implementation and later

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dropping for two reasons: lower demand because of decreasing subsequent fracture incidence, and savings from resources freed due to the refractures avoided. The increasing year-on-year QALY gain is explained by the sustained QALY benefit of a fracture avoided as its positive impact in terms of health utility gain would remain over the individual's lifespan.

The model proved uniquely useful to investigate the impact that specific configurations of FLSs would have on health outcomes as well as health and social care resources and costs. A scenario termed 'Perfect FLS' which assumed that FLSs would identify all fractured patients, treat them within 1 month, monitor them all, and achieve 100% adherence served as a reference benchmark against which the other effectively plausible configurations could be matched to. Whilst it may not represent a realistic scenario for most countries, this scenario does illustrate what countries considering FLS implementation could potentially achieve. We found that the extra costs per QALY gained under this configuration (£5,785) is in line with several publications reporting on the cost-effectiveness of FLSs (39), suggesting that they implicitly assume that these services can operate at that level. Otherwise, maximum fracture prevention was achieved if FLSs identified 100% of fractured patients, if they prescribed only injectable AOMs, or if they managed to lead to 100% adherence. In some cases, there were relevant trade-offs between these results and costs, such that prescribing only injectable AOMs would lead to the highest levels of additional costs. Whilst the lowest extra cost per QALY gained was achieved by FLSs if they only recommended the use of alendronate, they would reduce fractures by 27% less than FLSs prescribing injectables only. Treating only patients with hip/spine, or only with hip fractures would be expected to prevent more fractures and be cost saving compared to current practice, but at the cost of many less people benefiting from avoiding a fracture.

We observed that FLSs increase formal care at home in favour of reducing institutional stays, which could potentially place a higher burden on individuals or their families, including higher informal costs of social care and even productivity losses. Keeping people away from institutionalised care is, however, a sign that FLSs can safeguard the independence of people who avoid further fractures, which has a significant impact on their lives and that of their families.

However, this work is not without limitations. First, we modelled subsequent fractures only over a period of 5 years, which is not a realistic reflection of the time horizon of the impact of

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fractures on patients or FLSs to prevent subsequent ones. Although this was done mainly to prioritise accurate and available data on site- and sex-specific re-fracture rates, which rarely extends beyond a couple of years, it is also aligned with the time window of interest for decision makers in many settings. The model could be strengthened by covering the full expected lifetime of patients; notwithstanding this, examining the benefits and budget impact over the first five years of implementation can provide valuable insight for decision makers assessing the value of initiating FLS operations. Also, the model assumes an average re-fracture rate for all adults, which on average might lead to accurate results, but it is known that patients identified after a fracture are recommended treatment based on their risk of a further fracture and this varies depending on several patient-related variables. As a result, our findings likely underestimate the benefits of FLSs as these effectively operate by identifying patients at higher risk and treat them, which the model could simulate if a risk stratification were to be introduced. Another limitation adding to its conservative estimations of FLS benefit is the assumption that all simulated patients are treatment naïve when they enter the model. This is not the case in many developed countries where, especially people suffering from a hip fracture would have had some AOM treatment before. In those cases, model findings would underestimate fracture prevention and QALY benefit; however, in most other settings where secondary fracture prevention is weak, this assumption would be fitting. Further, many of the data required for the model were challenging to identify at the country level. Site- and sex-specific re-fracture rates were especially hard to find, especially in men, as was mortality by sex after non-hip fractures, discharge destinations for individuals with non-hip fractures especially after temporary rehabilitation, and adherence to therapy at 0, 4, 12 months and 5 years across the range of AOMs. The costs of informal care and of productivity loss were not included in this study but would be relevant to incorporate in a future version. Evidence about the use of informal care and the impact on productivity of fragility fractures is scarce but the model can incorporate these if they were available.

In conclusion, we have developed a flexible model that estimates the expected benefits and budget impact from FLS implementation, including the examination of different FLS configurations. Further work to develop country specific models is underway to delivery crucial national level data to inform the prioritisation of FLSs by policy makers.

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Tables

Table 1 – Selected key model input parameters for base case

	Men		Women		
Parameter	**Current practice**	**FLS**	**Current practice**	**FLS**	**Source**
Mean age at time of fragility fracture (years)					
After hip fracture	82		83		UK National Hip Fracture Database (NHFD)
After spine fracture	67		67		England Hospital Admitted Patient Care Activity, 2018-19 - Weighted mean for selected ICD codes
After other fracture	73		73		
Risk of subsequent fracture after hip fracture (10-year)					
Subsequent hip fracture	0.338		0.403		Population-based cohort study based on National Hospital Discharge Register (NHDR) of Denmark with follow up between 2002 and 2011 as published by Hansen et al, 2015
Subsequent spine fracture	0.031		0.047		
Subsequent other fracture	0.255		0.486		
Risk of subsequent fracture after spine fracture (10-year)					
Subsequent hip fracture	0.150		0.259		Population-based cohort study based on NHDR of Denmark with follow up between 2002 and 2011 as published by Hansen et al, 2015. Values for ‘other’ estimated by adding incidence of lower leg, femur, pelvis, forearm, and humerus
Subsequent spine fracture	0.202		0.176		
Subsequent other fracture	0.240		0.526		
Risk of subsequent fracture after other fracture (10-year)					
Subsequent hip fracture	0.127		0.204		Population-based cohort study based on NHDR of Denmark with follow up between 2002 and 2011 as published by Hansen et al, 2015. Values for ‘other’ fractures estimated as weighted average (2001 total counts) of lower leg, femur, pelvis, forearm and humerus.
Subsequent spine fracture	0.033		0.041		
Subsequent other fracture	0.382		0.548		
Probability of being identified					
After hip fracture	0.20	0.95	0.20	0.95	Key opinion leaders and expert opinion
After spine fracture	0.10	0.80	0.10	0.80	
After other fracture	0.10	0.80	0.10	0.80	

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Pharmacologic prescription after hip fracture					
Proportion of identified patients recommended treatment	0.40	0.85	0.60	0.85	Current practice: UK NHFD, Hawley et al (9). FLS: Oxford FLS database
Of those, proportion recommended alendronate	0.70	0.25	0.70	0.20	Key opinion leaders and expert opinion
Of those, proportion recommended risedronate	0.20	0.20	0.20	0.20	
Of those, proportion recommended denosumab	0.00	0.40	0.00	0.40	
Of those, proportion recommended zoledronate	0.10	0.15	0.10	0.15	
Of those, proportion recommended romosozumab	0.00	0.00	0.00	0.05	
Pharmacologic prescription after spine fracture					
Proportion of identified patients recommended treatment	0.05	0.80	0.10	0.80	Current practice: Key opinion leaders and expert opinion. FLS: 2019 Oxford FLS data
Of those, proportion recommended alendronate	0.60	0.30	0.60	0.30	Key opinion leaders and expert opinion
Of those, proportion recommended risedronate	0.40	0.20	0.40	0.20	
Of those, proportion recommended denosumab	0.00	0.24	0.00	0.20	
Of those, proportion recommended zoledronate	0.00	0.25	0.00	0.20	
Of those, proportion recommended teriparatide	0.00	0.01	0.00	0.02	
Of those, proportion recommended romosozumab	0.00	0.00	0.00	0.08	
Pharmacologic prescription after other fracture					
Proportion of identified patients recommended treatment	0.10	0.50	0.20	0.60	Key opinion leaders and expert opinion
Of those, proportion recommended alendronate	0.80	0.45	0.70	0.30	
Of those, proportion recommended risedronate	0.20	0.20	0.30	0.10	
Of those, proportion recommended denosumab	0.00	0.30	0.00	0.40	
Of those, proportion recommended zoledronate	0.00	0.05	0.00	0.15	
Of those, proportion recommended teriparatide	0.00	0.00	0.00	0.01	
Of those, proportion recommended romosozumab	0.00	0.00	0.00	0.04	
Treatment initiation					
Time between hip fracture and treatment start (months)	3	1	3	1	Current practice: UK NHFD. FLS: UK FLS Database
Time between spine fracture and treatment start (months)	6	2	6	2	Key opinion leaders and expert opinion
Time between other fracture and treatment start (months)	6	2	6	2	

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Healthcare after hip fracture		
Proportion admitted and having surgery	0.97	UK NHFD
Proportion admitted and not having surgery	0.03	
Proportion not admitted and seen only in clinic	0.00	
Healthcare after spine fracture		
Proportion to hospital (inpatient or outpatient)	0.10	Cooper et al (40)
Proportion managed in community	0.90	
Of those to hospital, proportion admitted + kyphoplasty	0.00	Key opinion leaders and expert opinion
Of those to hospital, proportion admitted + vertebroplasty	0.05	
Of those to hospital, proportion admitted + no procedure	0.10	
Of those to hospital, proportion not admitted + kyphoplasty	0.00	
Of those to hospital, proportion not admitted + vertebroplasty	0.05	
Of those to hospital, proportion not admitted + clinic only	0.80	
Healthcare after other fracture		
Proportion admitted and having surgery	0.25	Key opinion leaders and expert opinion
Proportion admitted and not having surgery	0.20	
Proportion not admitted and seen only in clinic	0.55	
Hospital costs		
A& E visit	£188	"Emergency Medicine, Category 2 Investigation with Category 1 Treatment" in National Schedule of NHS Costs Year: 2019-20 - All NHS trusts and NHS foundation trusts - HRG Data (currency VB08Z)
Clinic visit	£122	Total unit cost for "Trauma & Orthopaedics" including both consultant-led and non-consultant-led consultation, in National Schedule of NHS Costs Year: 2019-20 - All NHS trusts and NHS foundation trusts - Outpatient Attendances Data
Hip surgery	£6,520	Weighted average of non-elective long and short term stay unit cost of hip fracture with single or multiple intervention, in National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts
Vertebroplasty	£4,418	Weighted average of Total HRG unit cost of vertebroplasty (currencies = YH01Z, 2Z, 3Z), in National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts

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Surgery following fracture in other site	£1,957	Weighted average of Total HRG unit cost of pathological, arm, & rib fractures, in National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts
Community consultation cost for spine fracture	£67	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts, Community Health Services, Physiotherapist, Adult, One to One, currency = A08A1

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Table 2 – Health outcomes, resource use, and costs from FLS implementation

	Current practice	FLS	Absolute difference (FLS – current practice)
Health outcomes			
Re-fractures at 5 years			
Hip	59,112	54,318	**- 4,794**
Spine	16,494	14,449	**- 2,045**
Other	128,930	122,621	**- 6,309**
Total re-fractures	**204,537**	**191,388**	**- 13,149**
QALYs			
Not discounted	1,113,314	1,125,152	**11,838**
Discounted	1,103,803	1,115,512	**11,709**
Healthcare resource use			
Healthcare			
Hospital length of stay (days)	4,011,427	3,890,438	**- 120,989**
Surgical procedures (n)	228,409	221,954	**- 6,455**
Clinic appointments (n)	932,018	915,211	**- 16,807**
Temp rehabilitation (days)	2,470,335	2,407,535	**- 62,800**
FLS			
DXA scans (n)	2,374	69,224	**+66,850**
Lab tests (n)	7,324	108,484	**+101,160**
Full-time FLS administrators (n)	0	260	**+260**
Full-time doctors (n)	15	2	**- 13**
Full-time FLS coordinators (n)	0	537	**+537**
Radiographer (n)	0	7	**+7**
Social care			
Institutional care (patient years)	196,712	193,156	**- 3,556**
Ever in institutional care (n)	67,688	65,778	**- 1,910**
Costs (£)			
Healthcare			
A&E and inpatient (excl. surgery)	4,011,427	3,890,438	**- 120,989**
Surgical procedures	1,022,606,767	988,035,325	**- 34,571,442**
In/outpatient clinics	152,599,742	149,900,153	**- 2,699,589**
Temporary rehabilitation	1,168,468,387	1,138,764,802	**- 29,703,585**
Community consultations	72,008,899	69,823,609	**- 2,185,290**
Total healthcare costs	**2,419,695,222**	**2,350,414,327**	**- 69,280,895**
FLS			
FLS staff	1,003,606	22,007,262	**+21,003,656**
Laboratory tests	553,516	8,198,045	**+7,644,529**
DXA scans	253,848	7,406,960	**+7,153,112**
Medication (AOM)	637,317	167,898,576	**+167,261,259**
Total FLS costs	**2,448,287**	**205,510,843**	**+203,062,556**
Social care			
Formal care at home	15,340,695,704	15,434,078,126	**+93,382,422**
Long-term institutional care	7,194,928,999	7,064,937,757	**- 129,991,242**
Total social care costs	**22,535,624,703**	**22,499,015,883**	**- 36,608,820**
TOTAL COSTS			
Not discounted	24,957,768,212	25,054,941,053	**97,172,841**
Discounted	24,764,376,382	24,861,065,994	**96,689,612**

*: Discounting applied at 3.5% per year, which aggregates all costs at present value, i.e. 2021 GBP (£).

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Table 3 – Model results for different FLS configurations

			Fractures avoided			Extra costs *		Cost per QALY (£)
Scenario	**Re-fractures**	**FLS costs**	**(n)**	**(%)**	**QALYs gained ***	**(£)**	**(%)**	
Current practice	204,537	2,448,287						
FLS Base case	191,388	205,510,843	13,149	6.4%	11,709	£96,689,612	0.4%	£8,258
FLS Identification = 100%	188,506	244,524,326	16,031	7.8%	14,233	£112,821,690	0.5%	£7,927
FLS Treatment initiation = 1 month	190,766	208,550,407	13,771	6.7%	12,248	£98,892,137	0.4%	£8,074
FLS Monitoring = 100%	190,938	207,321,495	13,599	6.6%	12,033	£92,786,386	0.4%	£7,711
FLS Alendronate only	193,544	43,560,399	10,993	5.4%	10,388	-£84,678,852	-0.3%	§
FLS Injectables only (standard)	191,028	409,877,460	13,509	6.6%	11,491	£315,451,605	1.3%	£27,452
FLS Injectables only (max reduction)	189,426	778,702,903	15,111	7.4%	13,361	£657,372,205	2.6%	£49,201
FLS Adherence = 100%	189,652	216,548,270	14,885	7.3%	13,118	£92,545,143	0.4%	£7,055
FLS Perfect FLS	184,785	264,100,951	19,752	9.7%	17,543	£101,493,018	0.4%	£5,785
Current practice (hips & spines only)	29,380	1,045,192						
FLS Hips and spines only	25,519	75,012,233	3,861	13.1%	5,088	-£21,669,828	-0.3%	§
Current practice (hips only)	12,316	819,460						
FLS Hips only	11,144	38,741,202	1,172	9.5%	1,965	-£5,016,988	-0.1%	§

*: discounted at 3.5% per year

§: indicates “dominance”, i.e. that FLSs would lead to both QALY gains and overall cost reduction hence there is no ‘extra’ cost per QALY gained to be reported.

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Figure legends

Figure 1 – The figure describes the pathway of people having a sentinel fragility fracture of the hip, spine, or in another major site. Arrows indicate where patients can transition to, with the activities a Fracture Liaison Service potentially being initiated at any time either before or after hospital discharge. Patients can die at any point in the pathway.

Figure 2 – The bars in the figure indicate the excess total cost (i.e. health and social care costs as well as those required for FLS operation) in local currency of FLSs above the total cost under current practice per year. The orange line tracks the number of additional quality-adjusted life years gained by implementing FLSs (i.e. above those expected to be achieved without them) per year.

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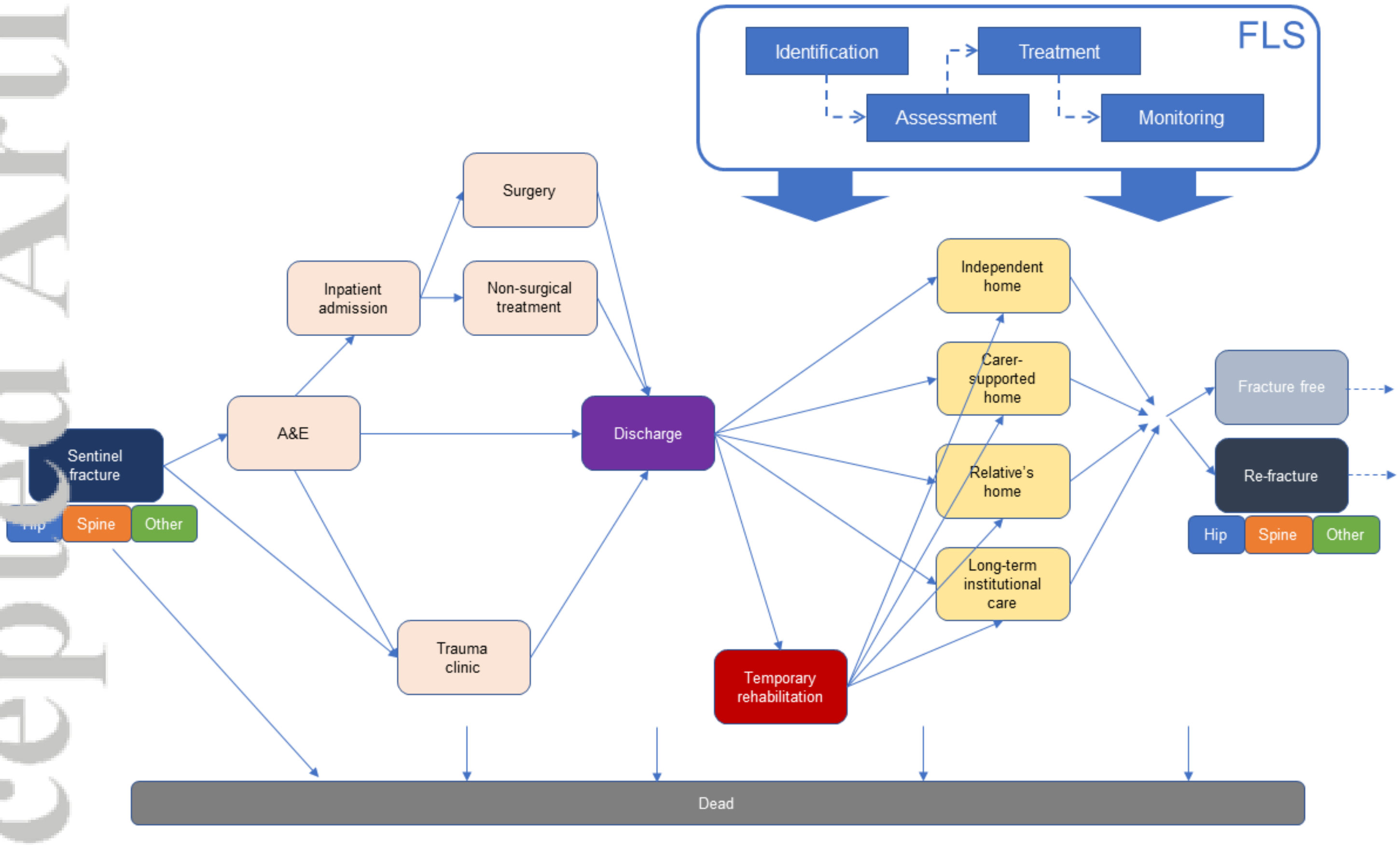

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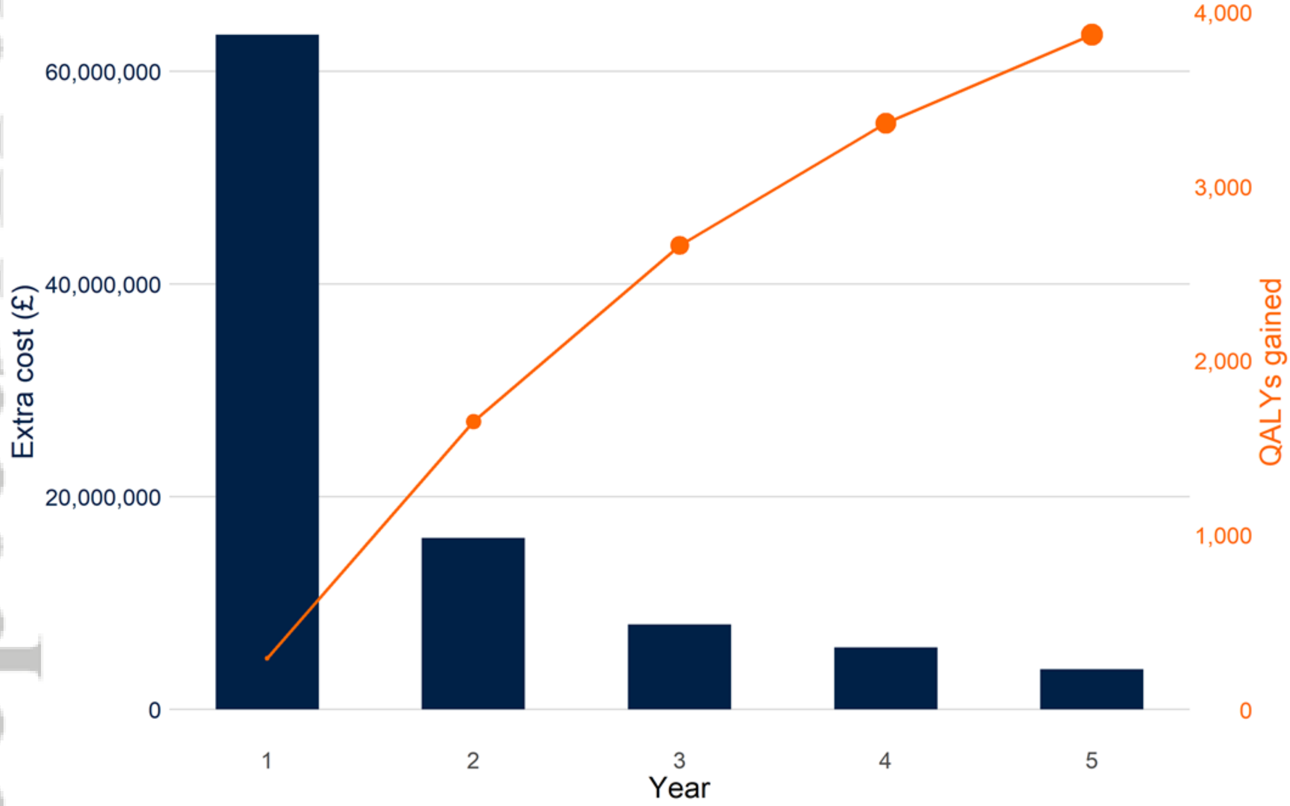

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